Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: The Idiopathic Pulmonary Fibrosis Clinical Research Network. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. N Engl J Med 2010;363:620-8. DOI: 10.1056/NEJMoa1002110.

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Section A: IPFnet clinical centers

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[1] Site enrolled patients into STEP-IPF

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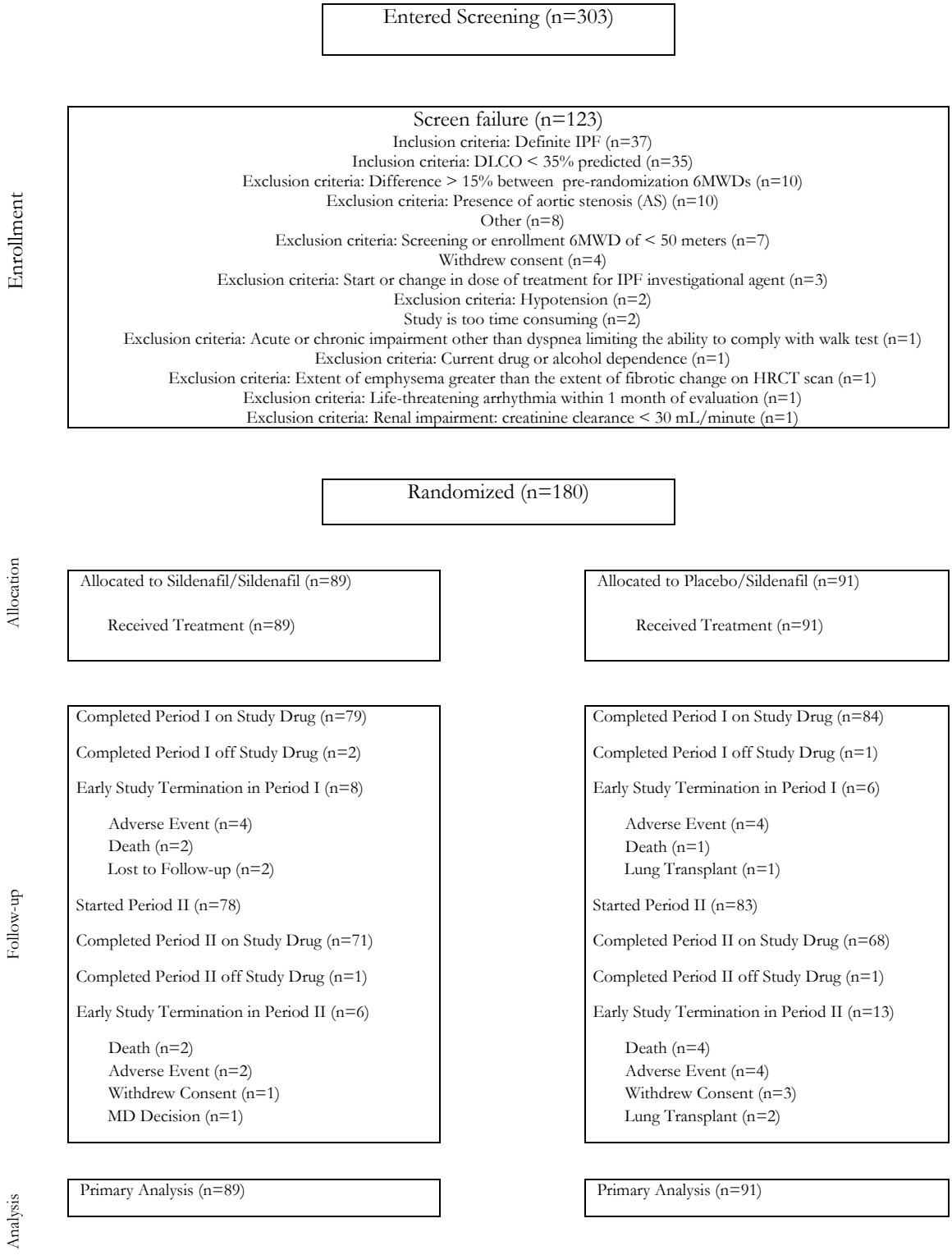
Section B: Expanded CONSORT Diagram



Section C: Tables

Table 1: Baseline Characteristics

Characteristic	Sildenafil/Sildenafil (N=89)	Placebo /Sildenafil (N=91)
Demographics		
Age (years)	69.76 ± 8.71	68.20 ± 9.25
Female gender (% of subjects)	15.7	17.6
Ethnicity: Hispanic or Latino (% of subjects)[1]	7.9	7.7
Race/ethnic group (% of subjects) [1]		
Caucasian	87.6	93.4
Black	5.6	1.1
Asian	3.4	2.2
Other	3.3	3.3
Smoking status (% of subjects)		
Ever smoked	76.4	75.8
Never smoked	23.6	24.2
Time since diagnosis (years)	2.03 ± 1.94	1.87 ± 1.93
Supplemental O2 used during walk (% of subjects)	31.5	26.4
2 L / min	14.6	19.8
4 L / min	15.7	5.5
6 L / min	1.1	1.1
Walk Distances		
1st 6 minute walk distance (meters)	246.93 ± 99.11	267.71 ± 127.75
% subjects w/walk distance < 150 meters	20.5	26.4
% subjects w/walk distance 150 – 249 meters	33.0	14.3
% subjects w/walk distance 250 – 349 meters	28.4	26.4
% subjects w/walk distance 350 – 449 meters	15.9	28.6
% subjects w/walk distance >= 450 meters	2.3	4.4
% subjects 1st walk > 1 min	97.8	98.9
% subjects 1st walk > 2 min	95.5	90.1
% subjects 1st walk > 3 min	88.8	78.0

% subjects 1st walk > 4 min	83.1	74.7
% subjects 1st walk > 5 min	78.7	72.5
% subjects 1st walk 6 min	75.3	69.2
2nd 6 minute walk distance (meters)	246.39 ± 103.40	269.55 ± 129.83
Walk distance < 150 meters	19.1	26.4
Walk distance 150 – 249 meters	36.0	14.3
Walk distance 250 – 349 meters	28.1	26.4
Walk distance 350 – 449 meters	12.4	26.4
Walk distance >= 450 meters	4.5	6.6
% subjects 2nd walk > 1 min	96.6	98.9
% subjects 2nd walk > 2 min	93.3	90.1
% subjects 2nd walk > 3 min	86.5	78.0
% subjects 2nd walk > 4 min	83.1	73.6
% subjects 2nd walk > 5 min	79.8	72.5
% subjects 2nd walk 6 min	75.3	71.4
Dyspnea		
Borg score, Post-walk (0-10, higher is worse)	3.82 ± 1.95	3.33 ± 1.73
UCSD questionnaire Total Score (0-120, higher is worse)*	50.71 ± 22.00	43.28 ± 20.18
Quality of Life		
SGRQ Total Score (0-100, higher is worse)	54.55 ± 16.46	51.72 ± 15.86
SGRQ Symptoms Score (0-100, higher is worse)	58.20 ± 17.75	53.99 ± 18.90
SGRQ Activity Score (0-100, higher is worse)	71.20 ± 17.50	68.02 ± 17.63
SGRQ Impacts Score (0-100, higher is worse)	43.20 ± 19.26	39.77 ± 18.81
SF-36 Aggregate Physical Score (0-100, higher is better)	33.17 ± 9.19	34.84 ± 8.69
SF-36 Aggregate Mental Score (0-100, higher is better)	49.53 ± 9.76	50.58 ± 9.52
SF-36 Bodily Pain Score (0-100, higher is better)	50.55 ± 10.98	49.72 ± 10.44
SF-36 General Health Score (0-100, higher is better)	36.99 ± 9.64	37.66 ± 8.73
SF-36 Mental Health Score (0-100, higher is better)	51.22 ± 9.07	50.95 ± 8.59
SF-36 Physical Functioning Score (0-100, higher is better)	29.20 ± 8.49	31.18 ± 8.31
SF-36 Role Emotional Score (0-100, higher is better)	45.13 ± 12.14	44.00 ± 13.60
SF-36 Role Physical Score (0-100, higher is better)	34.67 ± 11.39	36.38 ± 11.44
SF-36 Social Functioning Score (0-100, higher is better)	42.33 ± 10.88	43.06 ± 10.17

SF-36 Vitality Score (0-100, higher is better)	44.08 ± 9.28	45.30 ± 9.88
EQ-5D Score (-0.59-1.00, higher is better)	0.71 ± 0.24	0.74 ± 0.19
EQ-5D Visual Analog Scale (0-100, higher is better)	66.49 ± 17.45	67.66 ± 16.98
Pulmonary Physiology		
Forced vital capacity (% predicted)	54.89 ± 14.00	58.73 ± 14.12
Carbon monoxide diffusion capacity (% predicted)	25.81 ± 6.03	26.73 ± 6.16
Partial pressure of oxygen (mmHg)	66.22 ± 12.22	69.88 ± 12.85
Partial pressure of carbon dioxide (mmHg)	39.99 ± 5.25	38.53 ± 4.35
A-a gradient (mmHg)	29.74 ± 12.09	28.67 ± 13.26
SaO2 (% saturation)*	91.24 ± 4.22	92.59 ± 3.75

Plus-minus values are means ± SD
[1] Race and ethnicity were self-reported.
* Statistically significant difference

Table 2: Analyses of 6-Minute Walk Data (Baseline to 12 weeks)

	Sildenafil / Sildenafil % of subjects	Placebo / Sildenafil % of subjects	P Value
20% improvement from maximum baseline walk (primary endpoint)	**10.1**	**6.6**	**0.39**
20% improvement from mean baseline walk	16.9	7.7	0.06
20% improvement from 1st baseline walk	14.6	8.8	0.22
20% improvement from 2nd baseline walk	13.5	7.7	0.21
30 meter improvement from maximum baseline walk	15.7	14.3	0.79
30 meter improvement from mean baseline walk	19.1	15.4	0.51
30 meter improvement from 1st baseline walk	20.2	16.5	0.52
30 meter improvement from 2nd baseline walk	20.2	15.4	0.40
Any improvement from maximum baseline walk	34.8	24.2	0.12
Any improvement from mean baseline walk	44.9	30.8	0.05
Any improvement from 1st baseline walk	40.4	29.7	0.13
Any improvement from 2nd baseline walk	40.4	28.6	0.09
30 meter decline from maximum baseline walk [1]	46.1	52.7	0.37
30 meter decline from mean baseline walk [1]	43.8	47.3	0.64
30 meter decline from 1st baseline walk [1]	47.2	47.3	0.99
30 meter decline from 2nd baseline walk [1]	42.7	48.4	0.45
Unable to start 12 week walk (resting O2 desat)	5.6	6.6	0.78
12 week walk duration > 1 min	92.6	91.7	0.83
12 week walk duration > 2 min	84.0	78.6	0.38
12 week walk duration > 3 min	70.4	69.0	0.85
12 week walk duration > 4 min	64.2	61.9	0.76
12 week walk duration > 5 min	63.0	60.7	0.77
12 week walk duration 6 min	63.0	58.3	0.54
Mixed model analysis (compound symmetry) *	-28.52 (-43.24, -13.80)	-45.22 (-59.65, -30.79)	0.11
Mixed model analysis (unstructured) *	-29.51 (-50.83, -8.18)	-48.21 (-68.94, -27.49)	0.22

[1] In this decliner analysis, those unable to walk were consider to have had a 30 meter decline

* Estimated change (in meters) in 6MWD over 12 weeks estimate (95% CI)

Table 3: Longitudinal analysis of 6MWD, dyspnea, and QOL endpoints

Parameter Time Interval	Slope Estimate with 95% CI Sildenafil/Sildenafil	 Placebo/Sildenafil	Difference of Sildenafil/Sildenafil vs. Placebo/Sildenafil Estimate with 95% CI	 P-Value
6MWD				
Week 0 to 12	-28.52 (-43.24, -13.80)	-45.22 (-59.65, -30.79)	16.70 (-3.92, 37.32)	0.11
Week 12 to 24	-27.25 (-46.51, -8.00)	-16.95 (-36.35, 2.44)	-10.30 (-37.63, 17.03)	0.46
Dyspnea Questionnaires				
Borg Scale Post-Walk Rating				
Week 0 to 12	0.04 (-0.30, 0.37)	0.37 (0.04, 0.70)	-0.34 (-0.81, 0.14)	0.16
Week 12 to 24	0.33 (-0.05, 0.70)	0.08 (-0.30, 0.45)	0.25 (-0.28, 0.78)	0.35
UCSD Shortness of Breath Questionnaire Total				
Week 0 to 12	0.22 (-3.10, 3.54)	6.81 (3.53, 10.08)	-6.58 (-11.25, -1.92)	0.006
Week 12 to 24	5.67 (2.77, 8.57)	-0.77 (-3.70, 2.16)	6.44 (2.31, 10.56)	0.002
QOL Questionnaires				
St George's: Total Score				
Week 0 to 12	-1.64 (-3.91, 0.64)	2.45 (0.17, 4.72)	-4.08 (-7.30, -0.86)	0.01
Week 12 to 24	5.07 (3.18, 6.96)	0.95 (-0.98, 2.89)	4.12 (1.41, 6.82)	0.003
St George's: Symptoms Score				
Week 0 to 12	-3.58 (-7.02, -0.13)	2.15 (-1.30, 5.61)	-5.73 (-10.61, -0.85)	0.02
Week 12 to 24	5.61 (2.33, 8.90)	-0.18 (-3.50, 3.14)	5.79 (1.12, 10.47)	0.02
St George's: Activity Score				
Week 0 to 12	-1.15 (-3.68, 1.38)	2.49 (0.00, 4.99)	-3.64 (-7.20, -0.09)	0.04
Week 12 to 24	7.59 (5.37, 9.81)	0.99 (-1.30, 3.27)	6.60 (3.41, 9.79)	<.001
St George's: Impacts Score				
Week 0 to 12	-0.88 (-3.78, 2.02)	2.82 (-0.03, 5.67)	-3.70 (-7.76, 0.37)	0.07
Week 12 to 24	3.65 (0.97, 6.34)	1.02 (-1.70, 3.73)	2.64 (-1.18, 6.45)	0.18
SF 36 Aggregate Physical Score				
Week 0 to 12	-0.52 (-1.87, 0.83)	-0.35 (-1.69, 0.98)	-0.17 (-2.06, 1.73)	0.86
Week 12 to 24	-1.71 (-3.04, -0.39)	-0.38 (-1.68, 0.93)	-1.34 (-3.20, 0.53)	0.16
SF 36 Aggregate Mental Score				
Week 0 to 12	1.28 (-0.61, 3.16)	2.99 (1.12, 4.87)	-1.72 (-4.38, 0.94)	0.21
Week 12 to 24	-0.33 (-2.61, 1.95)	-0.21 (-2.44, 2.03)	-0.12 (-3.31, 3.06)	0.94
SF 36 Bodily Pain Score				

Week 0 to 12	-0.19 (-2.11, 1.73)	1.98 (0.09, 3.87)	-2.17 (-4.86, 0.52)	0.11
Week 12 to 24	-0.68 (-2.70, 1.33)	-1.31 (-3.33, 0.71)	0.63 (-2.23, 3.48)	0.67
SF 36 General Health Score				
Week 0 to 12	-1.04 (-2.52, 0.44)	-3.89 (-5.37, -2.42)	2.86 (0.76, 4.95)	0.008
Week 12 to 24	-1.59 (-3.00, -0.18)	1.12 (-0.30, 2.53)	-2.71 (-4.71, -0.71)	0.008
SF36 Mental Health Score				
Week 0 to 12	-0.15 (-1.80, 1.50)	-1.31 (-2.92, 0.31)	1.15 (-1.15, 3.46)	0.33
Week 12 to 24	0.26 (-1.55, 2.07)	-0.13 (-1.95, 1.69)	0.39 (-2.18, 2.96)	0.77
SF36 Physical Functioning Score				
Week 0 to 12	-0.94 (-2.25, 0.37)	-1.47 (-2.77, -0.18)	0.53 (-1.31, 2.37)	0.57
Week 12 to 24	-0.96 (-2.35, 0.43)	-0.79 (-2.18, 0.60)	-0.17 (-2.14, 1.80)	0.87
SF36 Role Emotional Score				
Week 0 to 12	-2.70 (-5.54, 0.14)	-4.80 (-7.61, -1.99)	2.10 (-1.90, 6.10)	0.30
Week 12 to 24	1.07 (-1.98, 4.12)	1.03 (-1.98, 4.04)	0.04 (-4.24, 4.32)	0.99
SF36 Role Physical Score				
Week 0 to 12	-0.88 (-2.86, 1.09)	-2.04 (-3.99, -0.09)	1.16 (-1.62, 3.93)	0.41
Week 12 to 24	-0.90 (-2.98, 1.18)	0.62 (-1.44, 2.69)	-1.52 (-4.45, 1.41)	0.31
SF36 Social Functioning Score				
Week 0 to 12	-0.70 (-3.00, 1.59)	-2.70 (-4.95, -0.44)	1.99 (-1.22, 5.21)	0.22
Week 12 to 24	-2.48 (-4.90, -0.06)	-0.38 (-2.80, 2.05)	-2.10 (-5.53, 1.32)	0.23
SF36 Vitality Score				
Week 0 to 12	0.02 (-1.71, 1.74)	-2.01 (-3.70, -0.32)	2.03 (-0.39, 4.44)	0.10
Week 12 to 24	-1.99 (-3.69, -0.30)	1.21 (-0.48, 2.91)	-3.21 (-5.60, -0.81)	0.009
EuroQoL Score				
Week 0 to 12	-0.01 (-0.06, 0.03)	-0.03 (-0.08, 0.01)	0.02 (-0.04, 0.08)	0.54
Week 12 to 24	-0.04 (-0.09, 0.01)	-0.04 (-0.09, 0.01)	0.00 (-0.07, 0.07)	0.97
EuroQoL Thermometer Response				
Week 0 to 12	0.48 (-3.10, 4.06)	-1.81 (-5.34, 1.73)	2.28 (-2.75, 7.32)	0.37
Week 12 to 24	-2.40 (-5.40, 0.61)	0.79 (-2.22, 3.80)	-3.19 (-7.44, 1.07)	0.14
Pulmonary Physiology				
FVC (% Predicted)				
Week 0 to 12	-0.97 (-2.00, 0.06)	-1.29 (-2.30, -0.28)	0.32 (-1.12, 1.76)	0.66
Week 12 to 24	-1.93 (-2.94, -0.91)	-1.59 (-2.63, -0.54)	-0.34 (-1.80, 1.12)	0.65
DLCO % Predicted				
Week 0 to 12	-0.33 (-1.36, 0.71)	-1.87 (-2.91, -0.83)	1.55 (0.08, 3.01)	0.04
Week 12 to 24	-1.51 (-2.54, -0.47)	0.80 (-0.27, 1.87)	-2.31 (-3.80, -0.81)	0.003
PaO2 (mmHg)				
Week 0 to 12	-0.63 (-2.41, 1.16)	-3.64 (-5.41, -1.87)	3.02 (0.50, 5.53)	0.02
Week 12 to 24	-2.25 (-3.91, -0.58)	-0.61 (-2.35, 1.13)	-1.64 (-4.05, 0.77)	0.18

PaCO2 (mmHg)				
Week 0 to 12	-0.01 (-0.75, 0.73)	-0.02 (-0.75, 0.71)	0.01 (-1.03, 1.05)	0.99
Week 12 to 24	-0.03 (-0.93, 0.87)	0.78 (-0.16, 1.72)	-0.81 (-2.11, 0.49)	0.22
A-a Gradient (mmHg)				
Week 0 to 12	0.41 (-1.54, 2.37)	2.95 (0.99, 4.92)	-2.54 (-5.31, 0.23)	0.07
Week 12 to 24	2.43 (0.40, 4.46)	0.02 (-2.14, 2.18)	2.41 (-0.55, 5.38)	0.11
SaO2 (%)				
Week 0 to 12	-0.17 (-1.02, 0.69)	-1.38 (-2.23, -0.52)	1.21 (0.00, 2.42)	0.05
Week 12 to 24	-0.64 (-1.40, 0.12)	-0.60 (-1.41, 0.20)	-0.04 (-1.14, 1.07)	0.95

Adjustment variables in the linear mixed models included baseline measures of age, gender, race, height, and DL_{CO}

Table 4: Serious Adverse Events by Study Period

Period 1 (0 – 12 weeks)

Body System Event Name	Sildenafil/Sildenafil N=89	Placebo/Sildenafil N=91	P-Value
Any Body System and Event	13 (14.6%) 14	15 (16.5%) 23	0.73
Respiratory, Thoracic and Mediastinal Disorders	7 (7.9%) 7	9 (9.9%) 11	0.63
Idiopathic Pulmonary Fibrosis	2 (2.2%) 2	5 (5.5%) 5	0.44
Dyspnoea	2 (2.2%) 2	1 (1.1%) 1	0.62
Respiratory Failure	1 (1.1%) 1	2 (2.2%) 2	0.99
Chronic Obstructive Pulmonary Disease	0 (0.0%) 0	1 (1.1%) 1	0.99
Hypoxemia	1 (1.1%) 1	0 (0.0%) 0	0.49
Pleural Effusion	0 (0.0%) 0	1 (1.1%) 1	0.99
Pneumothorax	0 (0.0%) 0	1 (1.1%) 1	0.99
Pulmonary Embolism	1 (1.1%) 1	0 (0.0%) 0	0.49
Infections and Infestations	3 (3.4%) 4	2 (2.2%) 2	0.68
Pneumonia	2 (2.2%) 2	1 (1.1%) 1	0.62
Bronchitis	0 (0.0%) 0	1 (1.1%) 1	0.99
Influenza	1 (1.1%) 1	0 (0.0%) 0	0.49
Viral Infection	1 (1.1%) 1	0 (0.0%) 0	0.49
Cardiac Disorders	1 (1.1%) 1	3 (3.3%) 3	0.62
Atrial Fibrillation	0 (0.0%) 0	2 (2.2%) 2	0.50
Cardiac Failure Congestive	1 (1.1%) 1	0 (0.0%) 0	0.49
Coronary Artery Disease	0 (0.0%) 0	1 (1.1%) 1	0.99
Gastrointestinal Disorders	2 (2.2%) 2	1 (1.1%) 1	0.62
Colitis Ischaemic	1 (1.1%) 1	0 (0.0%) 0	0.49
Intestinal Obstruction	0 (0.0%) 0	1 (1.1%) 1	0.99
Peptic Ulcer Haemorrhage	1 (1.1%) 1	0 (0.0%) 0	0.49
Hepatobiliary Disorders	0 (0.0%) 0	1 (1.1%) 1	0.99
Biliary Colic	0 (0.0%) 0	1 (1.1%) 1	0.99

Injury, Poisoning and Procedural Complications	0 (0.0%) 0	1 (1.1%) 3	0.99
Fall	0 (0.0%) 0	1 (1.1%) 1	0.99
Femur Fracture	0 (0.0%) 0	1 (1.1%) 1	0.99
Joint Injury	0 (0.0%) 0	1 (1.1%) 1	0.99
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	0 (0.0%) 0	1 (1.1%) 1	0.99
Neoplasm Malignant	0 (0.0%) 0	1 (1.1%) 1	0.99
Nervous System Disorders	0 (0.0%) 0	1 (1.1%) 1	0.99
Convulsion	0 (0.0%) 0	1 (1.1%) 1	0.99

Period 2 (12 – 24 weeks)

Body System Event Name	Sildenafil/Sildenafil N=78	Placebo/Sildenafil N=83	P-Value
Any Body System and Event	12 (15.4%) 19	12 (14.5%) 14	0.87
Respiratory, Thoracic and Mediastinal Disorders	5 (6.4%) 6	7 (8.4%) 7	0.63
Idiopathic Pulmonary Fibrosis	1 (1.3%) 1	4 (4.8%) 4	0.37
Pulmonary Embolism	2 (2.6%) 2	1 (1.2%) 1	0.61
Dyspnoea	1 (1.3%) 1	1 (1.2%) 1	0.99
Respiratory Failure	2 (2.6%) 2	0 (0.0%) 0	0.23
Pulmonary Hypertension	0 (0.0%) 0	1 (1.2%) 1	0.99
Infections and Infestations	3 (3.8%) 3	3 (3.6%) 3	0.99
Pneumonia	3 (3.8%) 3	3 (3.6%) 3	0.99
Cardiac Disorders	4 (5.1%) 4	0 (0.0%) 0	0.05
Cardiac Arrest	1 (1.3%) 1	0 (0.0%) 0	0.48
Cardio-Respiratory Arrest	1 (1.3%) 1	0 (0.0%) 0	0.48
Cor Pulmonale Acute	1 (1.3%) 1	0 (0.0%) 0	0.48
Coronary Artery Disease	1 (1.3%) 1	0 (0.0%) 0	0.48
Metabolism and Nutrition Disorders	1 (1.3%) 1	1 (1.2%) 1	0.99
Hyponatraemia	1 (1.3%) 1	1 (1.2%) 1	0.99

Nervous System Disorders	1 (1.3%) 1	1 (1.2%) 1	0.99
Cerebral Infarction	1 (1.3%) 1	0 (0.0%) 0	0.48
Syncope	0 (0.0%) 0	1 (1.2%) 1	0.99
Ear and Labyrinth Disorders	0 (0.0%) 0	1 (1.2%) 1	0.99
Vertigo	0 (0.0%) 0	1 (1.2%) 1	0.99
General Disorders and Administration Site Conditions	0 (0.0%) 0	1 (1.2%) 1	0.99
Multi-Organ Failure	0 (0.0%) 0	1 (1.2%) 1	0.99
Investigations	1 (1.3%) 1	0 (0.0%) 0	0.48
Blood Potassium Increased	1 (1.3%) 1	0 (0.0%) 0	0.48
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	1 (1.3%) 1	0 (0.0%) 0	0.48
Gastric Cancer	1 (1.3%) 1	0 (0.0%) 0	0.48
Vascular Disorders	1 (1.3%) 2	0 (0.0%) 0	0.48
Aortic Aneurysm	1 (1.3%) 1	0 (0.0%) 0	0.48
Venous Thrombosis	1 (1.3%) 1	0 (0.0%) 0	0.48

Summarization format N_{PAT} (xx.x%) N_{AE}, where N_{PAT} is the number of patients with at least one AE, xx.x% = N_{PAT} divided by the total number of randomized patients times 100, and N_{AE} is the number of AEs observed.

Table 5: Adverse Event Summary

Body System Event Name	Sildenafil N=89	Placebo N=91	All Patients N=180	P-Value
Any Body System and Event	80 (89.9%) 442	79 (86.8%) 453	159 (88.3%) 895	0.52
Respiratory, Thoracic and Mediastinal Disorders	46 (51.7%) 85	52 (57.1%) 86	98 (54.4%) 171	0.46
Dyspnoea	21 (23.6%) 27	20 (22.0%) 23	41 (22.8%) 50	0.80
Cough	13 (14.6%) 13	11 (12.1%) 11	24 (13.3%) 24	0.62
Progression of Idiopathic Pulmonary Fibrosis	3 (3.4%) 3	10 (11.0%) 11	13 (7.2%) 14	0.05
Nasal Congestion	3 (3.4%) 3	5 (5.5%) 5	8 (4.4%) 8	0.72
Productive Cough	5 (5.6%) 5	3 (3.3%) 3	8 (4.4%) 8	0.49
Epistaxis	4 (4.5%) 4	3 (3.3%) 3	7 (3.9%) 7	0.72
Dyspnoea Exertional	2 (2.2%) 2	4 (4.4%) 6	6 (3.3%) 8	0.68
Respiratory Failure	4 (4.5%) 4	2 (2.2%) 2	6 (3.3%) 6	0.44
Haemoptysis	2 (2.2%) 2	3 (3.3%) 3	5 (2.8%) 5	0.99
Sinus Congestion	2 (2.2%) 2	3 (3.3%) 3	5 (2.8%) 5	0.99
Pulmonary Embolism	3 (3.4%) 5	1 (1.1%) 1	4 (2.2%) 6	0.37
Wheezing	2 (2.2%) 2	2 (2.2%) 2	4 (2.2%) 4	0.99
Hypoxia	2 (2.2%) 2	0 (0.0%) 0	2 (1.1%) 2	0.24
Pleural Effusion	1 (1.1%) 1	1 (1.1%) 1	2 (1.1%) 2	0.99
Postnasal Drip	0 (0.0%) 0	2 (2.2%) 2	2 (1.1%) 2	0.50
Rhinorrhoea	0 (0.0%) 0	2 (2.2%) 2	2 (1.1%) 2	0.50
Infections and Infestations	42 (47.2%) 58	39 (42.9%) 52	81 (45.0%) 110	0.56
Upper Respiratory Tract Infection	17 (19.1%) 20	13 (14.3%) 14	30 (16.7%) 34	0.39
Pneumonia	8 (9.0%) 8	7 (7.7%) 9	15 (8.3%) 17	0.75
Bronchitis	4 (4.5%) 4	6 (6.6%) 6	10 (5.6%) 10	0.75
Urinary Tract Infection	1 (1.1%) 1	5 (5.5%) 5	6 (3.3%) 6	0.21
Sinusitis	3 (3.4%) 5	2 (2.2%) 2	5 (2.8%) 7	0.68
Herpes Zoster	2 (2.2%) 2	2 (2.2%) 2	4 (2.2%) 4	0.99
Influenza	2 (2.2%) 3	2 (2.2%) 2	4 (2.2%) 5	0.99
Nasopharyngitis	2 (2.2%) 2	2 (2.2%) 3	4 (2.2%) 5	0.99
Rhinitis	1 (1.1%) 1	1 (1.1%) 1	2 (1.1%) 2	0.99
Nervous System Disorders	35 (39.3%) 56	35 (38.5%) 58	70 (38.9%) 114	0.91
Headache	23 (25.8%) 31	26 (28.6%) 32	49 (27.2%) 63	0.68
Dizziness	12 (13.5%) 14	11 (12.1%) 11	23 (12.8%) 25	0.78
Syncope	4 (4.5%) 4	3 (3.3%) 3	7 (3.9%) 7	0.72
Convulsion	1 (1.1%) 1	1 (1.1%) 2	2 (1.1%) 3	0.99
Sinus Headache	1 (1.1%) 1	1 (1.1%) 1	2 (1.1%) 2	0.99
Tremor	1 (1.1%) 1	1 (1.1%) 1	2 (1.1%) 2	0.99
Gastrointestinal Disorders	32 (36.0%) 45	27 (29.7%) 43	59 (32.8%) 88	0.37
Diarrhoea	14 (15.7%) 16	13 (14.3%) 14	27 (15.0%) 30	0.79
Nausea	5 (5.6%) 5	7 (7.7%) 9	12 (6.7%) 14	0.58
Gastrooesophageal Reflux Disease	4 (4.5%) 4	5 (5.5%) 5	9 (5.0%) 9	0.99
Dyspepsia	5 (5.6%) 5	3 (3.3%) 3	8 (4.4%) 8	0.50
Constipation	3 (3.4%) 3	2 (2.2%) 3	5 (2.8%) 6	0.68
Vomiting	2 (2.2%) 2	3 (3.3%) 4	5 (2.8%) 6	0.99
Abdominal Distension	2 (2.2%) 2	0 (0.0%) 0	2 (1.1%) 2	0.24
General Disorders and Administration Site Conditions	27 (30.3%) 45	26 (28.6%) 44	53 (29.4%) 89	0.80
Oedema Peripheral	15 (16.9%) 18	12 (13.2%) 17	27 (15.0%) 35	0.49
Fatigue	5 (5.6%) 8	9 (9.9%) 11	14 (7.8%) 19	0.29
Pyrexia	4 (4.5%) 5	4 (4.4%) 5	8 (4.4%) 10	0.99

Chills	4 (4.5%) 5	1 (1.1%) 1	5 (2.8%) 6	0.21
Chest Discomfort	3 (3.4%) 3	1 (1.1%) 1	4 (2.2%) 4	0.37
Non-Cardiac Chest Pain	1 (1.1%) 2	3 (3.3%) 3	4 (2.2%) 5	0.62
Musculoskeletal and Connective Tissue Disorders	25 (28.1%) 34	20 (22.0%) 33	45 (25.0%) 67	0.34
Back Pain	3 (3.4%) 4	3 (3.3%) 4	6 (3.3%) 8	0.99
Myalgia	3 (3.4%) 3	3 (3.3%) 3	6 (3.3%) 6	0.99
Pain in Extremity	2 (2.2%) 2	4 (4.4%) 6	6 (3.3%) 8	0.68
Arthralgia	4 (4.5%) 4	1 (1.1%) 3	5 (2.8%) 7	0.21
Musculoskeletal Chest Pain	5 (5.6%) 5	0 (0.0%) 0	5 (2.8%) 5	0.03
Neck Pain	1 (1.1%) 1	4 (4.4%) 5	5 (2.8%) 6	0.37
Muscle Spasms	4 (4.5%) 4	0 (0.0%) 0	4 (2.2%) 4	0.06
Muscular Weakness	1 (1.1%) 1	2 (2.2%) 2	3 (1.7%) 3	0.99
Joint Swelling	1 (1.1%) 1	1 (1.1%) 1	2 (1.1%) 2	0.99
Muscle Twitching	1 (1.1%) 1	1 (1.1%) 1	2 (1.1%) 2	0.99
Musculoskeletal Pain	1 (1.1%) 1	1 (1.1%) 1	2 (1.1%) 2	0.99
Osteopenia	1 (1.1%) 1	1 (1.1%) 1	2 (1.1%) 2	0.99
Tendonitis	1 (1.1%) 3	1 (1.1%) 1	2 (1.1%) 4	0.99
Vascular Disorders	15 (16.9%) 19	13 (14.3%) 16	28 (15.6%) 35	0.64
Flushing	3 (3.4%) 4	9 (9.9%) 9	12 (6.7%) 13	0.08
Hypotension	6 (6.7%) 6	4 (4.4%) 4	10 (5.6%) 10	0.53
Hypertension	2 (2.2%) 2	2 (2.2%) 2	4 (2.2%) 4	0.99
Orthostatic Hypotension	1 (1.1%) 1	1 (1.1%) 1	2 (1.1%) 2	0.99
Skin and Subcutaneous Tissue Disorders	12 (13.5%) 21	14 (15.4%) 15	26 (14.4%) 36	0.72
Rash	2 (2.2%) 3	1 (1.1%) 1	3 (1.7%) 4	0.62
Actinic Keratosis	2 (2.2%) 3	0 (0.0%) 0	2 (1.1%) 3	0.24
Ecchymosis	0 (0.0%) 0	2 (2.2%) 3	2 (1.1%) 3	0.50
Eczema	2 (2.2%) 2	0 (0.0%) 0	2 (1.1%) 2	0.24
Hyperhidrosis	0 (0.0%) 0	2 (2.2%) 2	2 (1.1%) 2	0.50
Pruritus	0 (0.0%) 0	2 (2.2%) 2	2 (1.1%) 2	0.50
Rash Erythematous	1 (1.1%) 1	1 (1.1%) 1	2 (1.1%) 2	0.99
Telangiectasia	2 (2.2%) 3	0 (0.0%) 0	2 (1.1%) 3	0.24
Cardiac Disorders	11 (12.4%) 15	13 (14.3%) 15	24 (13.3%) 30	0.70
Palpitations	2 (2.2%) 4	4 (4.4%) 4	6 (3.3%) 8	0.68
Coronary Artery Disease	2 (2.2%) 2	1 (1.1%) 2	3 (1.7%) 4	0.62
Tachycardia	1 (1.1%) 1	2 (2.2%) 2	3 (1.7%) 3	0.99
Atrial Fibrillation	0 (0.0%) 0	2 (2.2%) 2	2 (1.1%) 2	0.50
Cardiac Failure Congestive	2 (2.2%) 2	0 (0.0%) 0	2 (1.1%) 2	0.24
Sinus Tachycardia	1 (1.1%) 2	1 (1.1%) 1	2 (1.1%) 3	0.99
Investigations	10 (11.2%) 11	13 (14.3%) 18	23 (12.8%) 29	0.54
Weight Decreased	2 (2.2%) 2	3 (3.3%) 3	5 (2.8%) 5	0.99
Cardiac Murmur	3 (3.4%) 3	0 (0.0%) 0	3 (1.7%) 3	0.12
Blood Uric Acid Increased	0 (0.0%) 0	2 (2.2%) 2	2 (1.1%) 2	0.50
White Blood Cell Count Increased	0 (0.0%) 0	2 (2.2%) 2	2 (1.1%) 2	0.50
Psychiatric Disorders	6 (6.7%) 7	16 (17.6%) 21	22 (12.2%) 28	0.03
Insomnia	2 (2.2%) 2	6 (6.6%) 7	8 (4.4%) 9	0.28
Depression	2 (2.2%) 2	4 (4.4%) 4	6 (3.3%) 6	0.68
Anxiety	2 (2.2%) 2	3 (3.3%) 3	5 (2.8%) 5	0.99
Abnormal Dreams	1 (1.1%) 1	2 (2.2%) 2	3 (1.7%) 3	0.99
Eye Disorders	12 (13.5%) 17	9 (9.9%) 10	21 (11.7%) 27	0.45
Vision Blurred	5 (5.6%) 6	5 (5.5%) 6	10 (5.6%) 12	0.99
Cataract	1 (1.1%) 1	1 (1.1%) 1	2 (1.1%) 2	0.99
Conjunctivitis	2 (2.2%) 2	0 (0.0%) 0	2 (1.1%) 2	0.24
Metabolism and Nutrition Disorders	5 (5.6%) 5	11 (12.1%) 16	16 (8.9%) 21	0.13
Anorexia	0 (0.0%) 0	4 (4.4%) 4	4 (2.2%) 4	0.12
Hyponatraemia	2 (2.2%) 2	1 (1.1%) 3	3 (1.7%) 5	0.62
Decreased Appetite	0 (0.0%) 0	2 (2.2%) 2	2 (1.1%) 2	0.50
Gout	1 (1.1%) 1	1 (1.1%) 1	2 (1.1%) 2	0.99

Hyperglycaemia	1 (1.1%) 1	1 (1.1%) 1	2 (1.1%) 2	0.99
Hypoglycaemia	1 (1.1%) 1	1 (1.1%) 1	2 (1.1%) 2	0.99
Blood and Lymphatic System Disorders	7 (7.9%) 7	2 (2.2%) 2	9 (5.0%) 9	0.10
Anaemia	4 (4.5%) 4	2 (2.2%) 2	6 (3.3%) 6	0.44
Ear and Labyrinth Disorders	5 (5.6%) 5	3 (3.3%) 5	8 (4.4%) 10	0.49
Vertigo	3 (3.4%) 3	1 (1.1%) 2	4 (2.2%) 5	0.37
Injury, Poisoning and Procedural Complications	3 (3.4%) 5	4 (4.4%) 6	7 (3.9%) 11	0.99
Fall	1 (1.1%) 1	2 (2.2%) 2	3 (1.7%) 3	0.99
Renal and Urinary Disorders	3 (3.4%) 3	4 (4.4%) 5	7 (3.9%) 8	0.99
Pollakiuria	0 (0.0%) 0	3 (3.3%) 4	3 (1.7%) 4	0.25
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	2 (2.2%) 2	3 (3.3%) 3	5 (2.8%) 5	0.99
Hepatobiliary Disorders	0 (0.0%) 0	2 (2.2%) 3	2 (1.1%) 3	0.50
Reproductive System and Breast Disorders	1 (1.1%) 1	1 (1.1%) 1	2 (1.1%) 2	0.99

Summarization format N_{PAT} (xx.x%) N_{AE}, where N_{PAT} is the number of patients with at least one AE, xx.x% = N_{PAT} divided by the total number of randomized patients times 100, and N_{AE} is the number of AEs observed. Only AEs occurring in greater than 1% of the study population are listed.

Table 6: Exclusionary medications (containing nitrates)

Nitroglycerin
Deponit (transdermal)
Minitran
Nitrek
Nitro-BID (and Nitro-BID ointment)
Nitrodisc
Nitro-DUR
Nitrogard
Nitroglyn
Nitrolingual (spray)
Nitrol ointment (APPLI-KIT)
Nitrong
Nitro-Par Nitrostat
Nitro-Time
Transderm-Nitro

Isosorbide mononitrate
Imdur
Ismo
Monoket (tablets)

Isosorbide dinitrate
Dilatrate-SR
Isordil
Sorbitrate

Erythatyl tetranitrate

Pentaerythritol tetranitrate

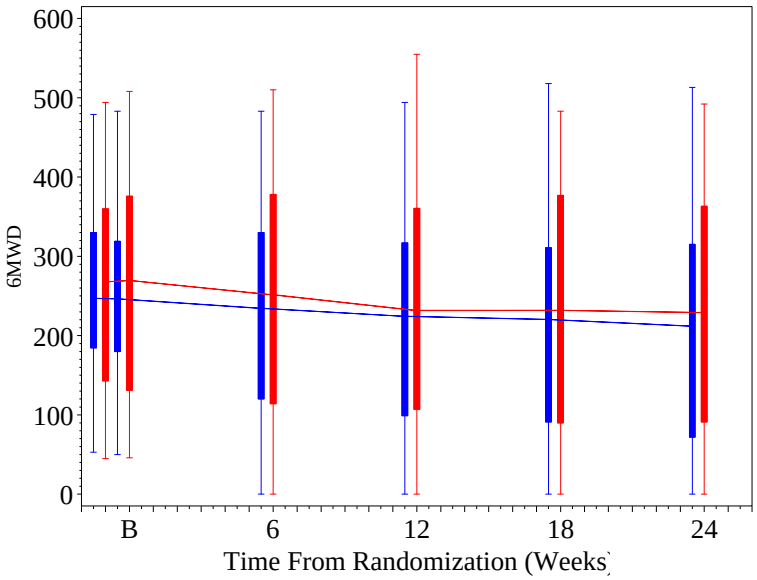
Sodium nitroprusside

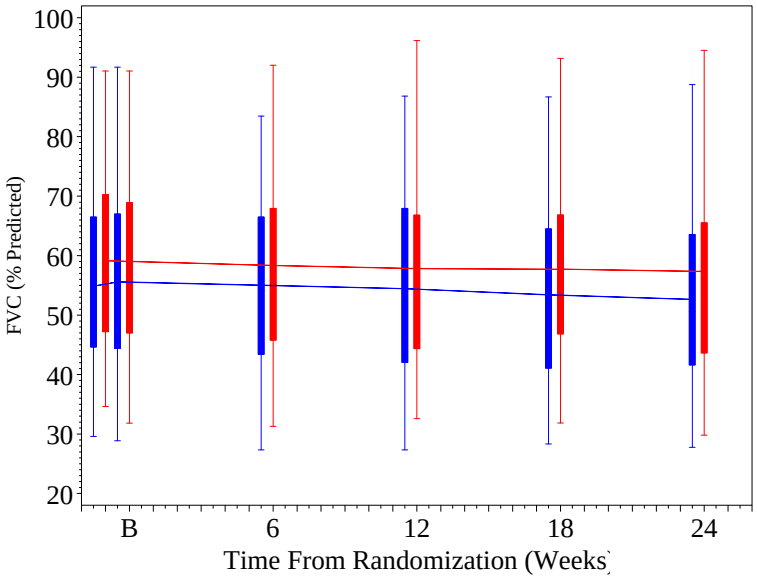
Source: http://www.medicinenet.com/script/main/art.asp?articlekey=8229

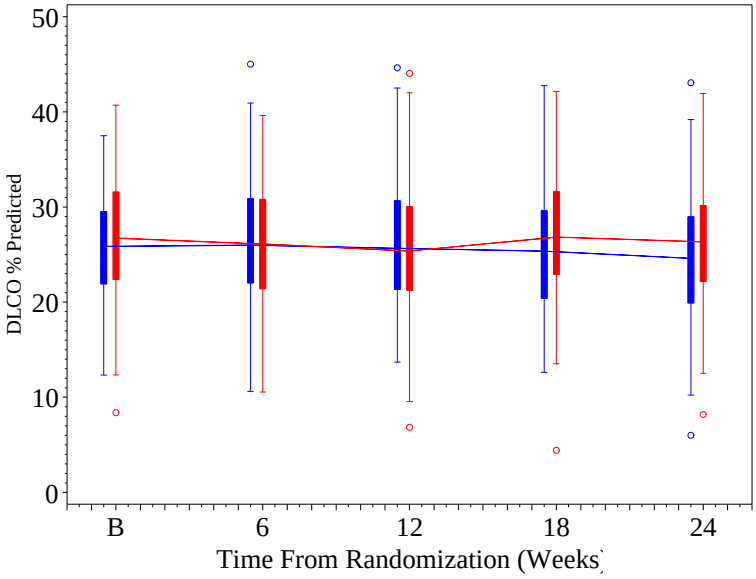
Section D: Box Plots Showing the Primary and Secondary Findings

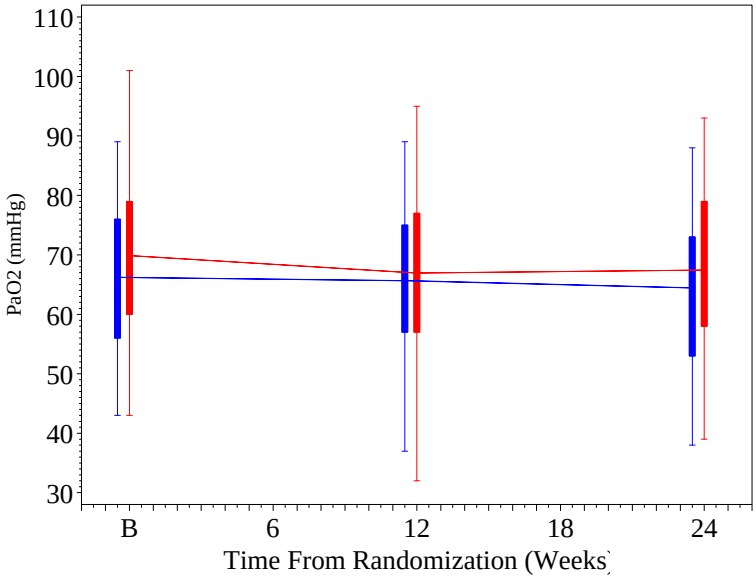
Blue: Sildenafil / Sildenafil Red: Placebo / Sildenafil

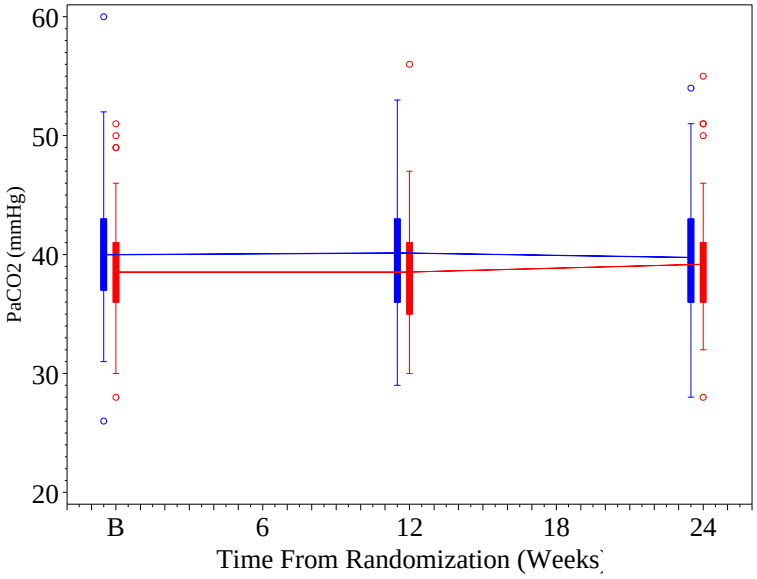
Boxes represent 25th to 75th percentiles. Whiskers represent 1.5 X interquartile range. Lines connect the means across time.

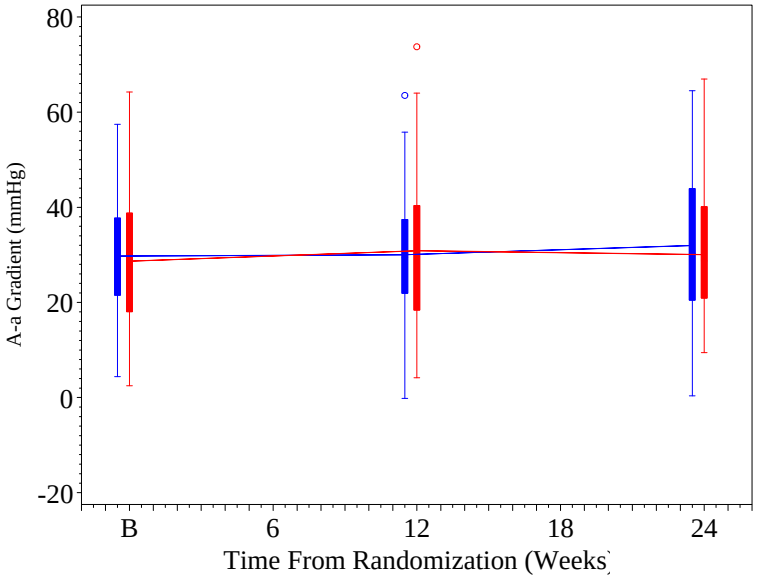


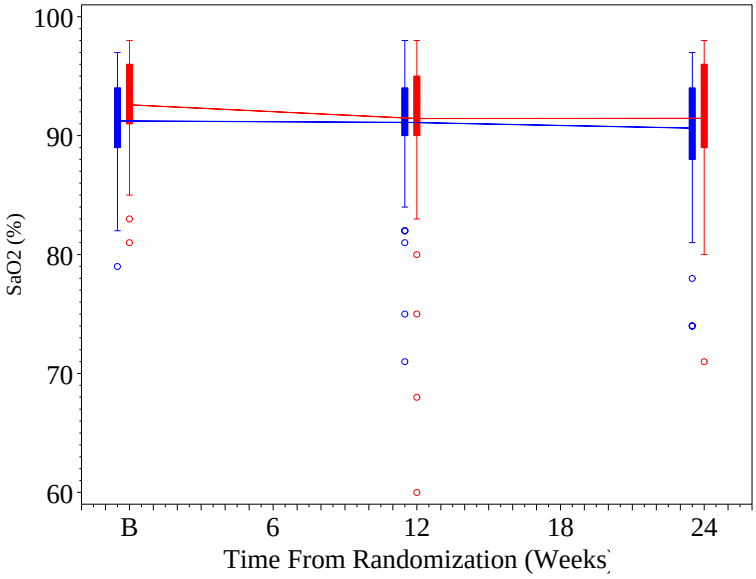


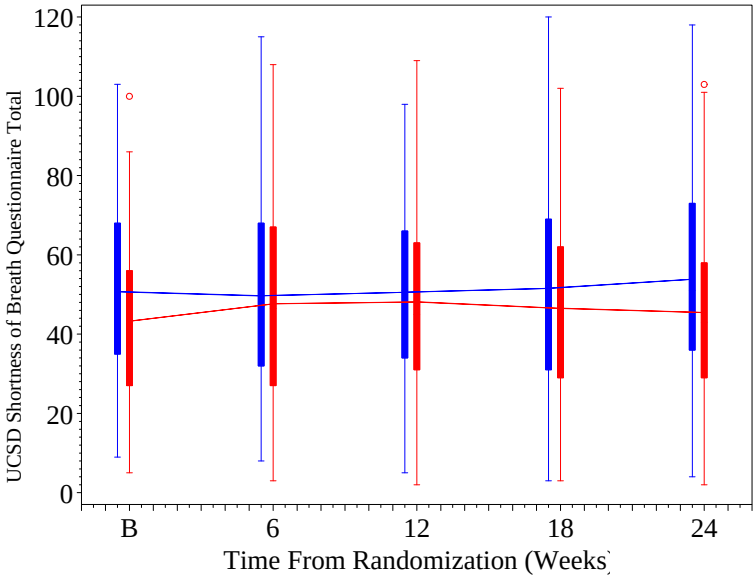

DLCO % Predicted
50
40
30
20
10
0
B
6
12
18
24
Time From Randomization (Weeks)

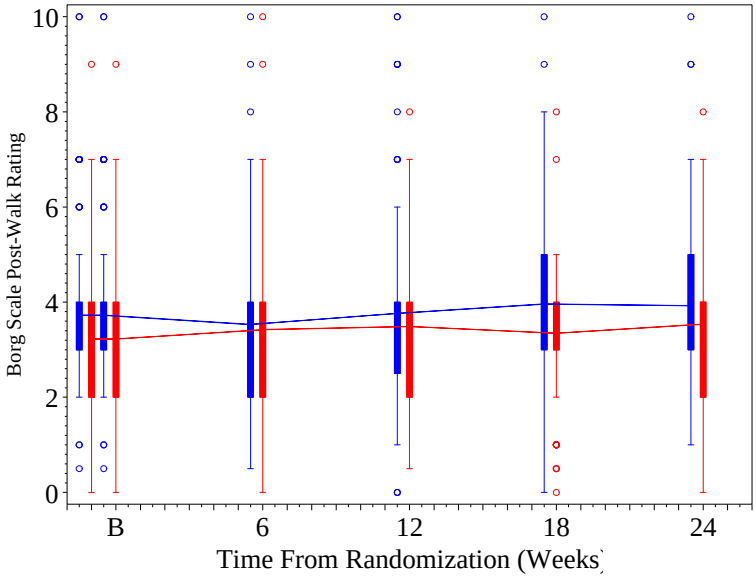

PaO2 (mmHg)
110
100
90
80
70
60
50
40
30
B
6
12
18
24
Time From Randomization (Weeks)

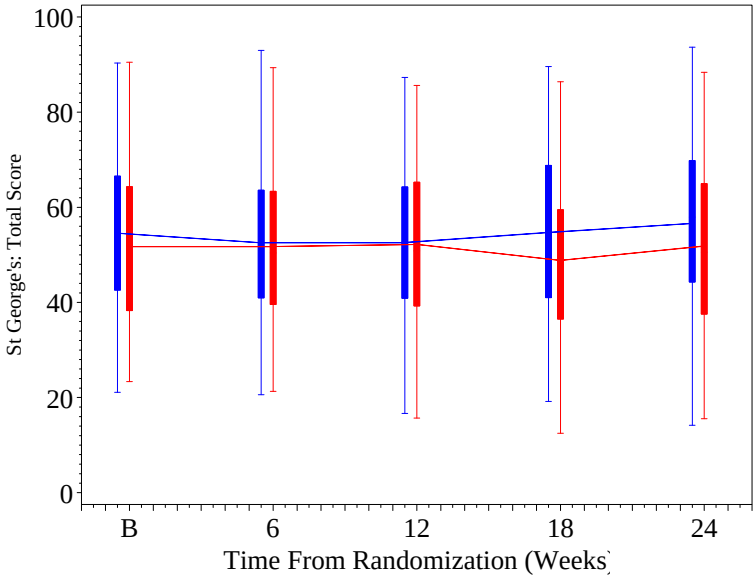

60
50
40
30
20
PaCO2 (mmHg)
B
6
12
18
24
Time From Randomization (Weeks)

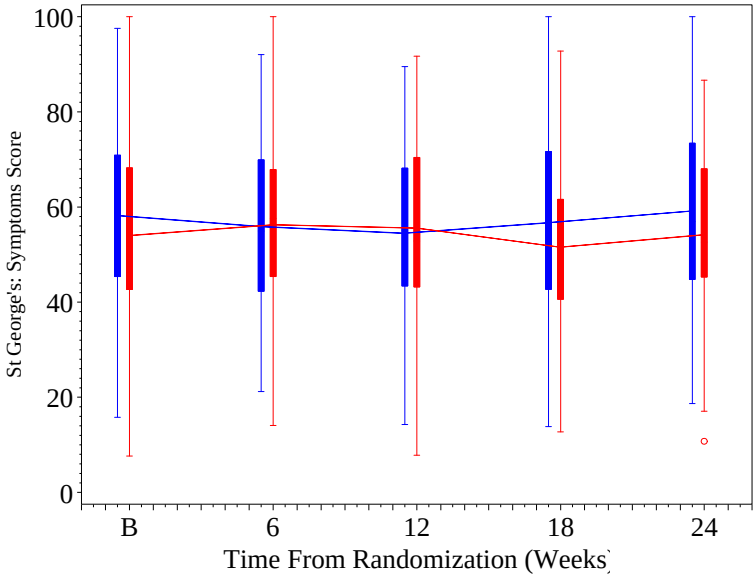

80
60
40
20
0
-20
A-a Gradient (mmHg)
B
6
12
18
24
Time From Randomization (Weeks)

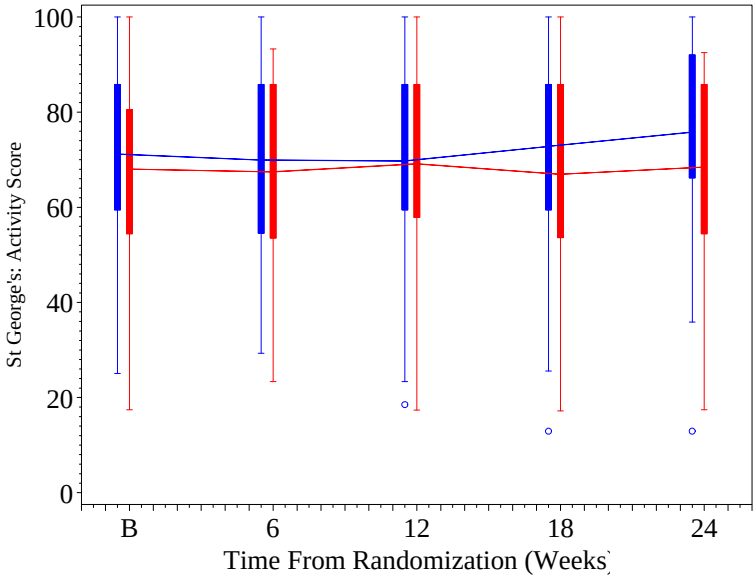

100
90
80
70
60
SaO2 (%)
B
6
12
18
24
Time From Randomization (Weeks)

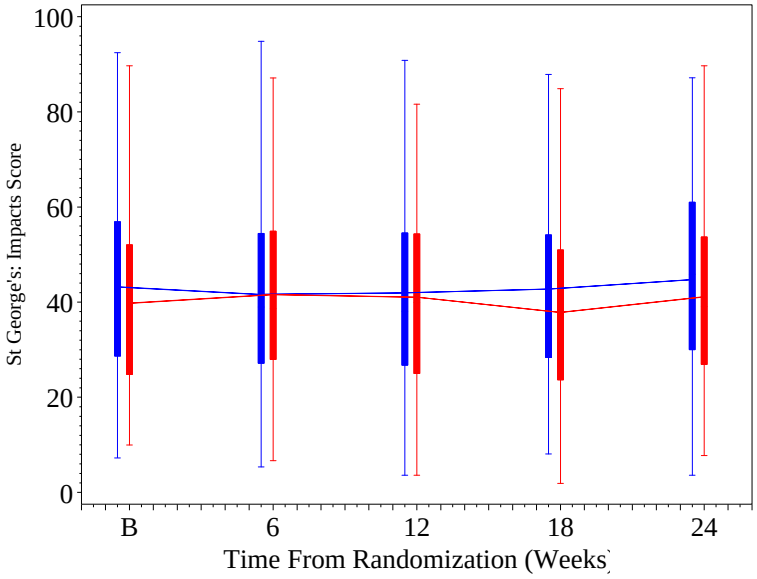

120
100
80
60
40
20
0
UCSD Shortness of Breath Questionnaire Total
B
6
12
18
24
Time From Randomization (Weeks)

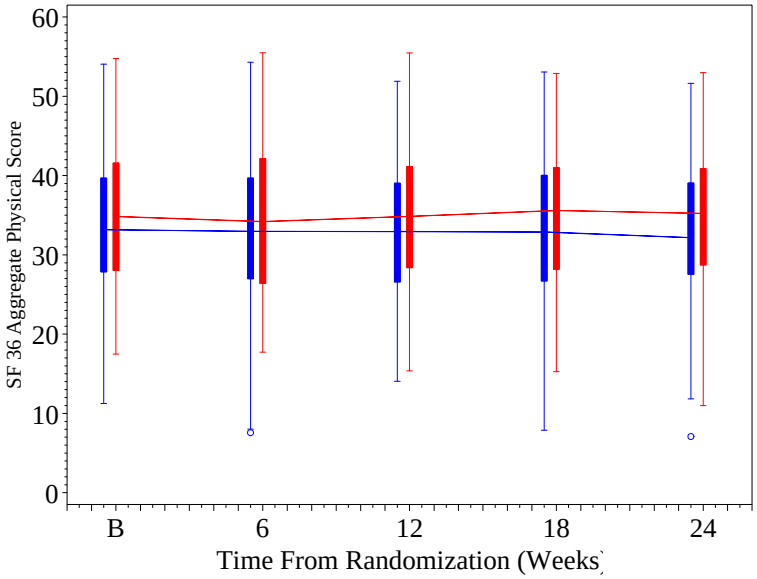

Borg Scale Post-Walk Rating
10
8
6
4
2
0
B
6
12
18
24
Time From Randomization (Weeks)

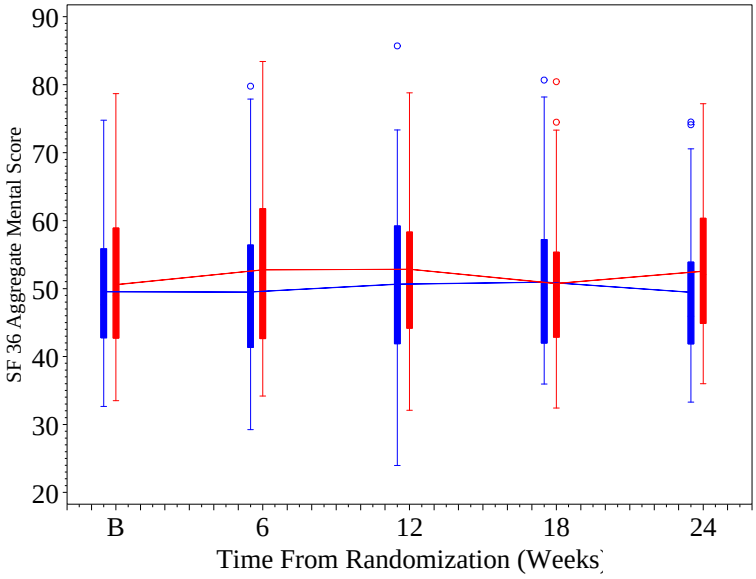

St George's: Total Score
100
80
60
40
20
0
B
6
12
18
24
Time From Randomization (Weeks)

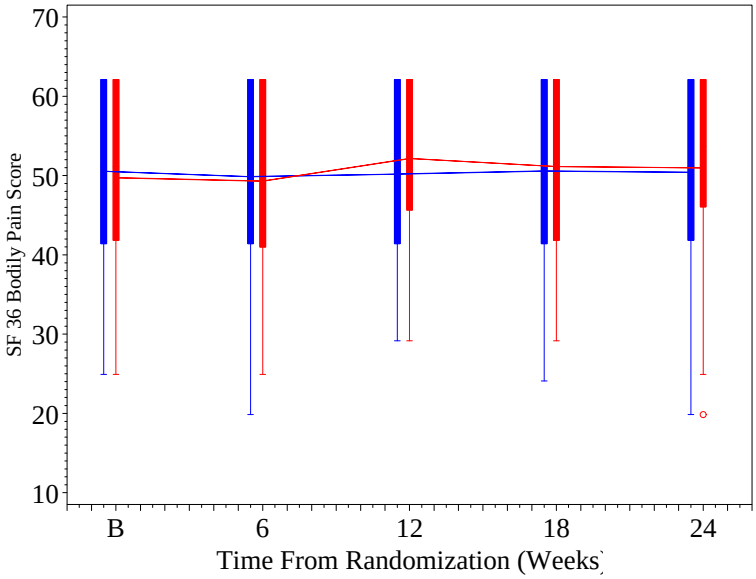

St George's: Symptoms Score
100
80
60
40
20
0
B
6
12
18
24
Time From Randomization (Weeks)

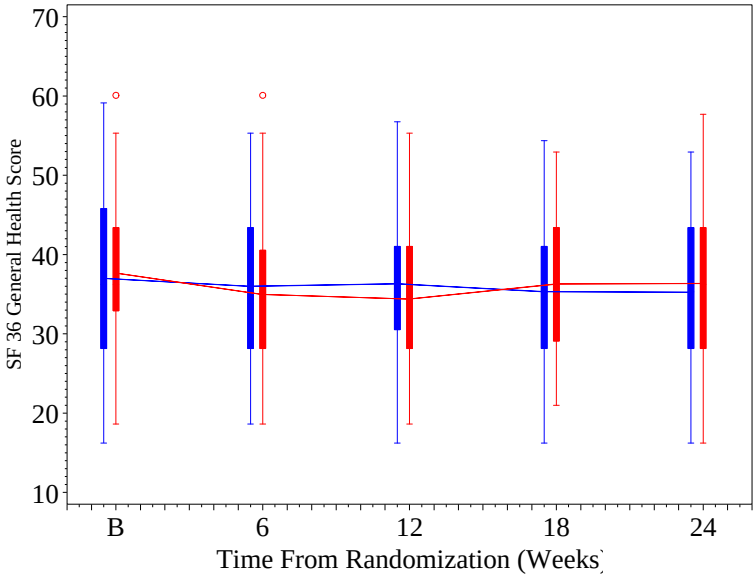

St George's: Activity Score
100
80
60
40
20
0
B
6
12
18
24
Time From Randomization (Weeks)

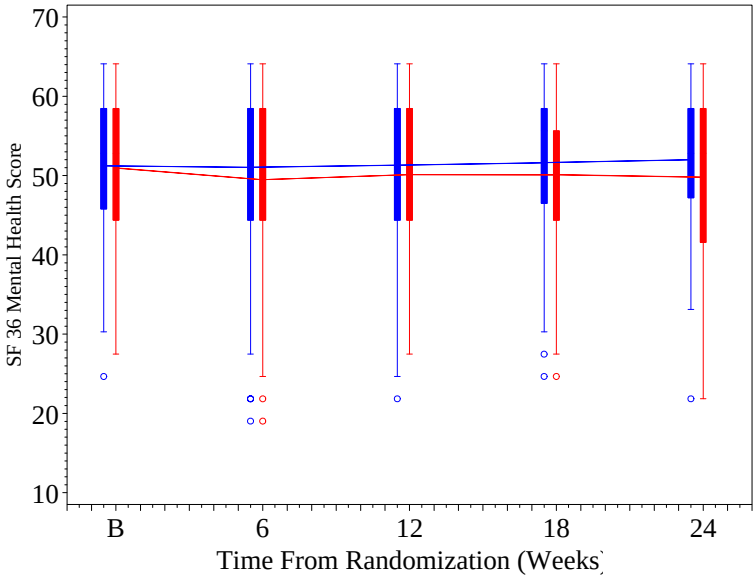

St George's: Impacts Score
100
80
60
40
20
0
B
6
12
18
24
Time From Randomization (Weeks)

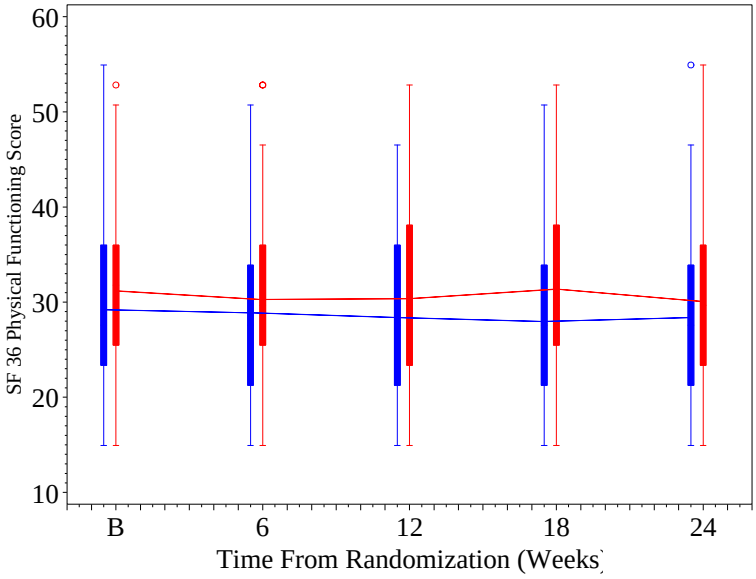

SF 36 Aggregate Physical Score
60
50
40
30
20
10
0
B
6
12
18
24
Time From Randomization (Weeks)

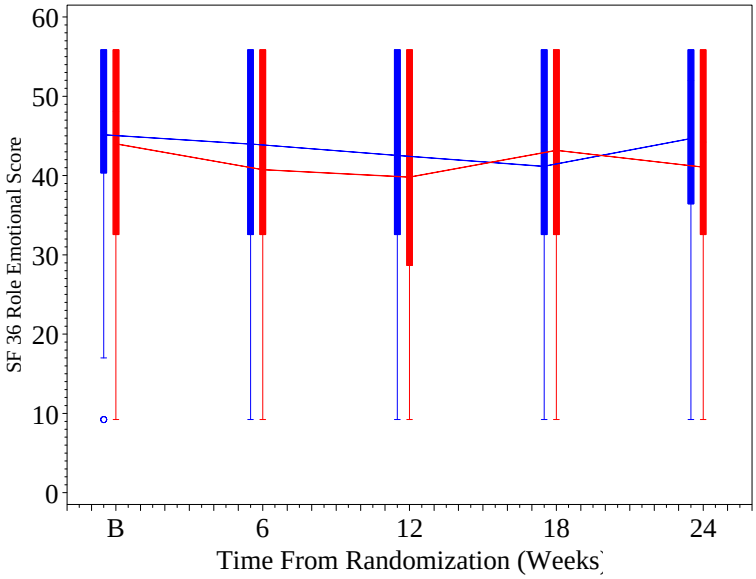

SF 36 Aggregate Mental Score
90
80
70
60
50
40
30
20
B
6
12
18
24
Time From Randomization (Weeks)

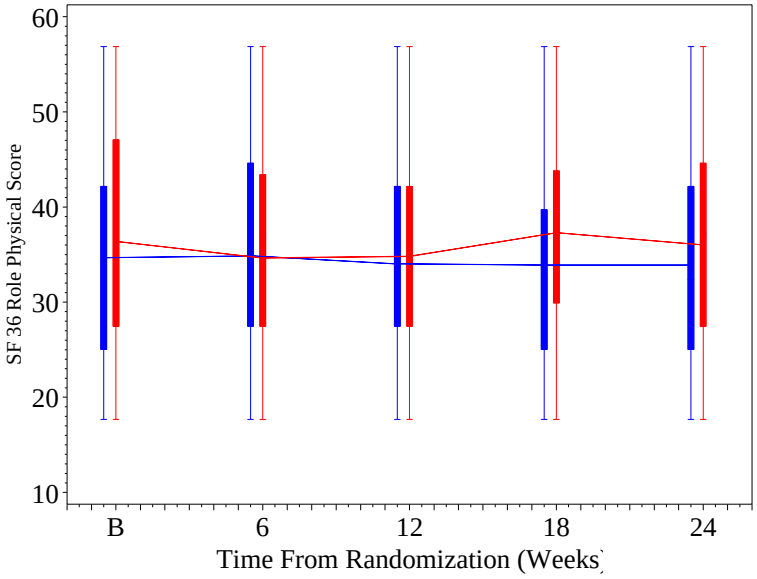

SF 36 Bodily Pain Score
70
60
50
40
30
20
10
B
6
12
18
24
Time From Randomization (Weeks)

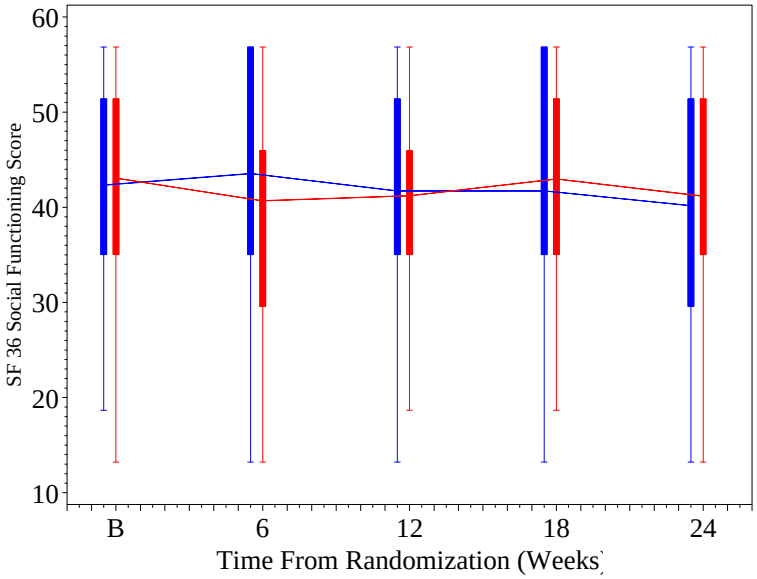

70
60
50
40
30
20
10
SF 36 General Health Score
B
6
12
18
24
Time From Randomization (Weeks)

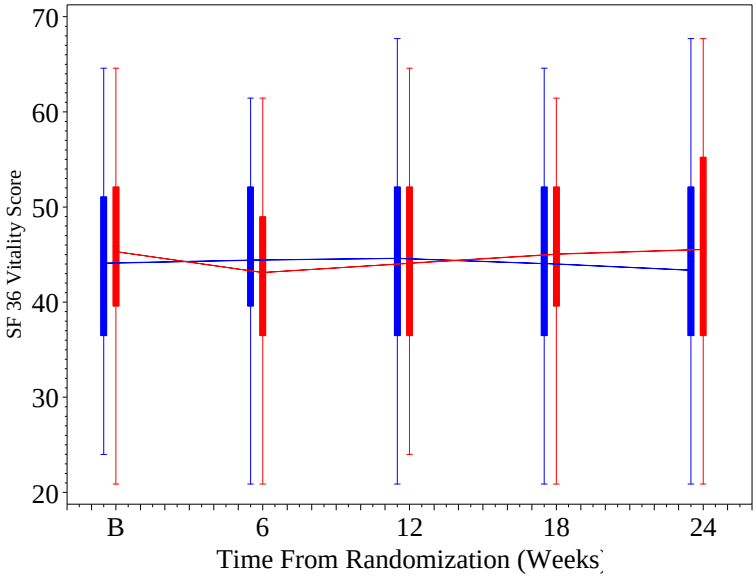

70
60
50
40
30
20
10
SF 36 Mental Health Score
B
6
12
18
24
Time From Randomization (Weeks)

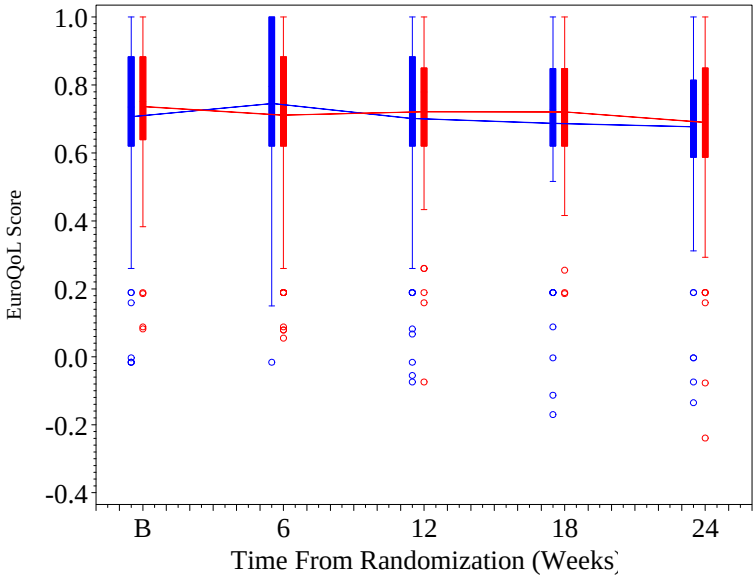

60
50
40
30
20
10
SF 36 Physical Functioning Score
B
6
12
18
24
Time From Randomization (Weeks)

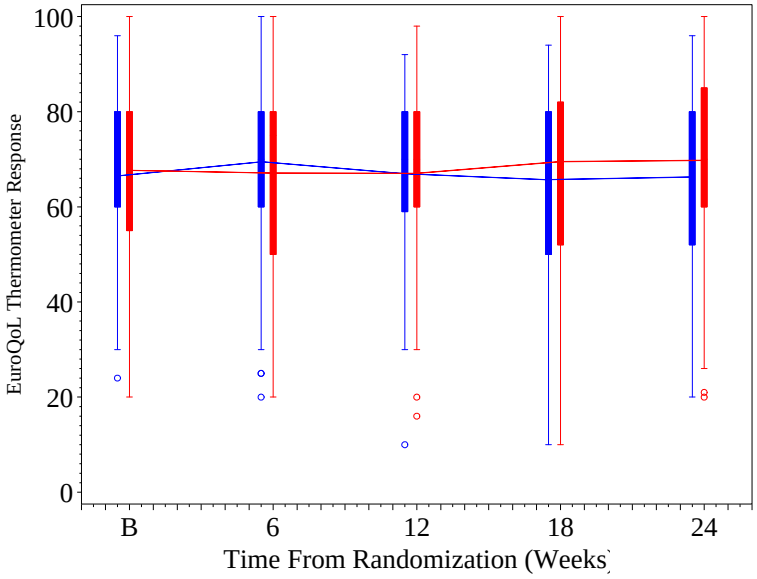

60
50
40
30
20
10
0
SF 36 Role Emotional Score
B
6
12
18
24
Time From Randomization (Weeks)


60
50
40
30
20
10
SF 36 Role Physical Score
B
6
12
18
24
Time From Randomization (Weeks)


60
50
40
30
20
10
SF 36 Social Functioning Score
B
6
12
18
24
Time From Randomization (Weeks)


70
60
50
40
30
20
SF 36 Vitality Score
B
6
12
18
24
Time From Randomization (Weeks)

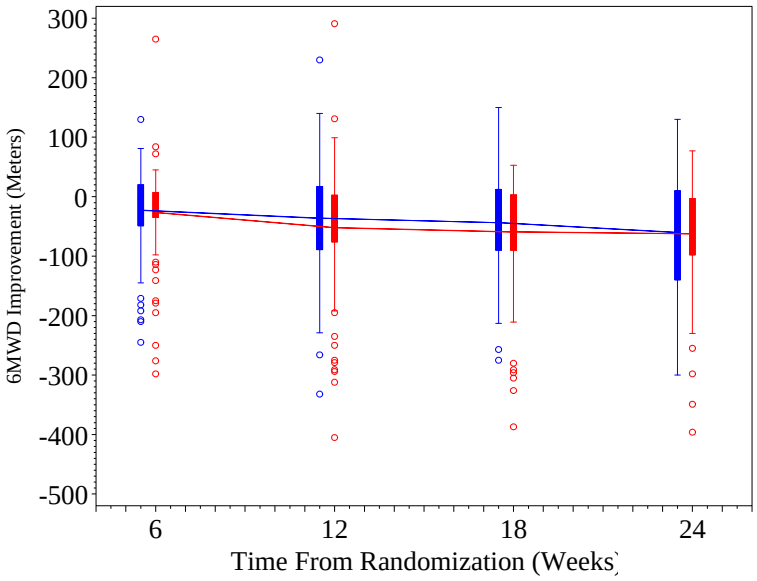

1.0
0.8
0.6
0.4
0.2
0.0
-0.2
-0.4
EuroQoL Score
B
6
12
18
24
Time From Randomization (Weeks)

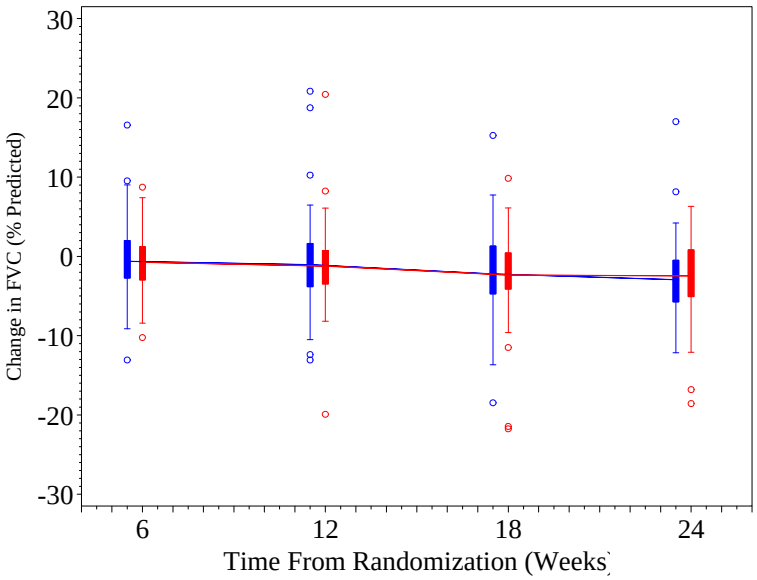

100
80
60
40
20
0
EuroQoL Thermometer Response
B
6
12
18
24
Time From Randomization (Weeks)

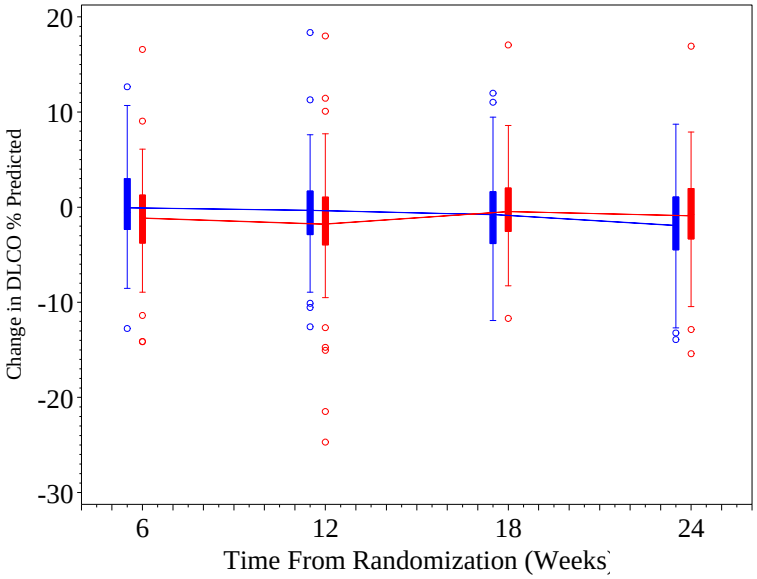
Section E: Box Plots Showing Changes from Baseline in Outcome Variables

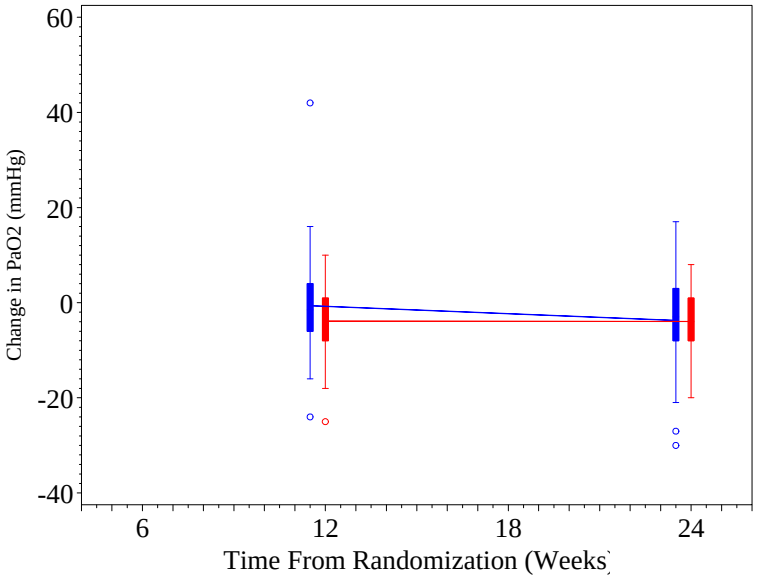
Blue: Sildenafil / Sildenafil Red: Placebo / Sildenafil

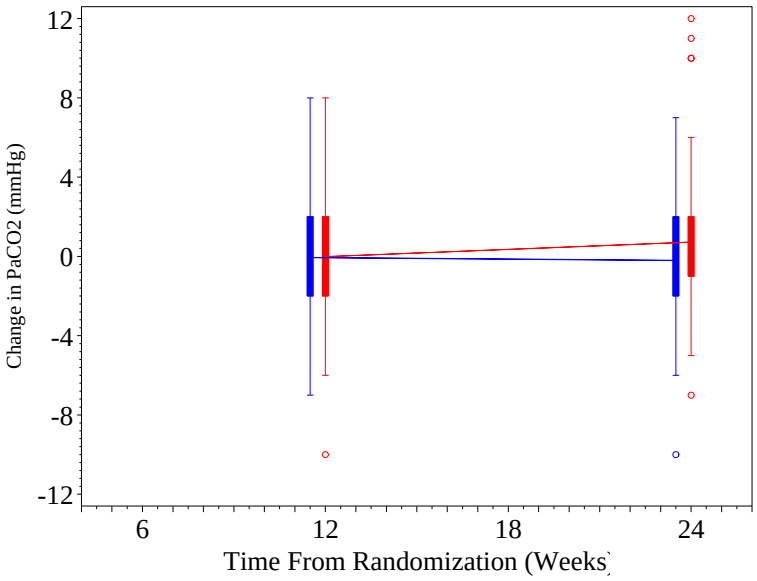
Boxes represent 25th to 75th percentiles. Whiskers represent 1.5 X interquartile range. Lines connect the means across time.

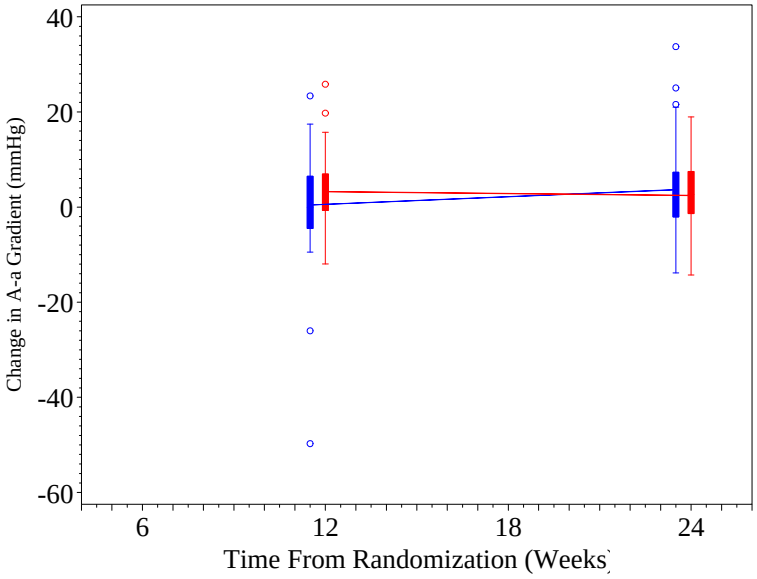


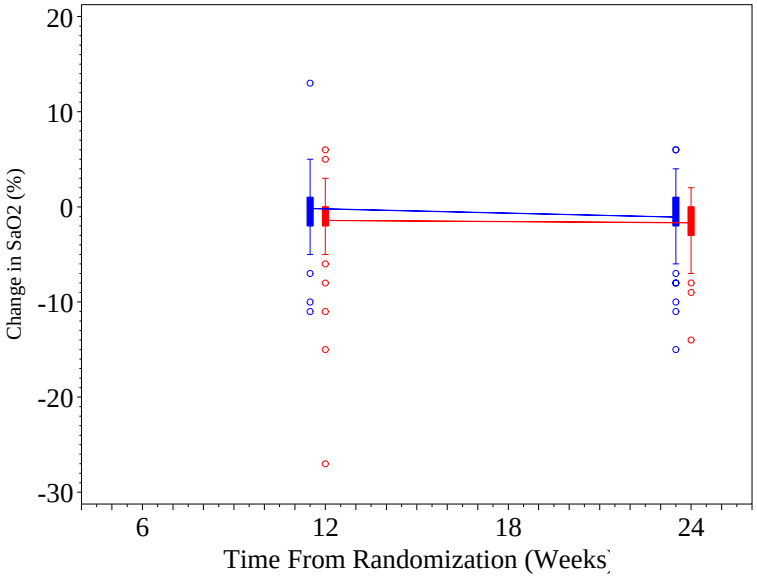


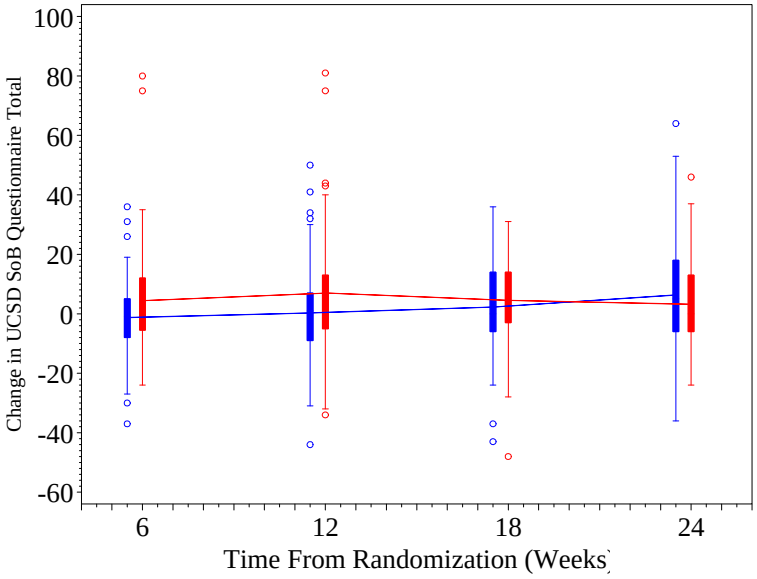

20
10
0
-10
-20
-30
Change in DLCO % Predicted
6
12
18
24
Time From Randomization (Weeks)

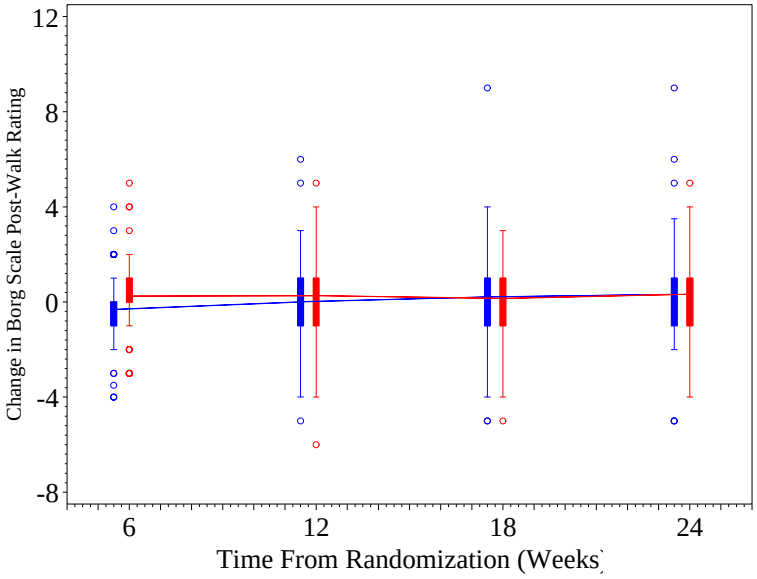

60
40
20
0
-20
-40
Change in PaO2 (mmHg)
6
12
18
24
Time From Randomization (Weeks)

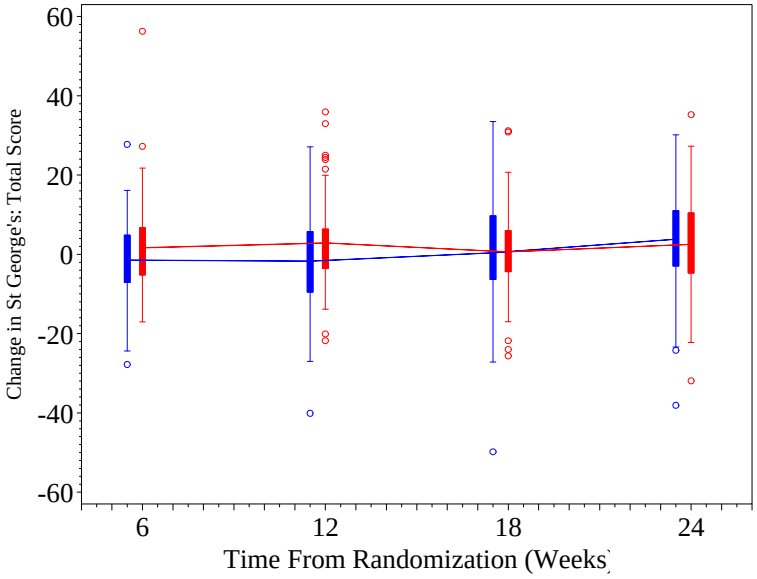

12
8
4
0
-4
-8
-12
Change in PaCO2 (mmHg)
6
12
18
24
Time From Randomization (Weeks)

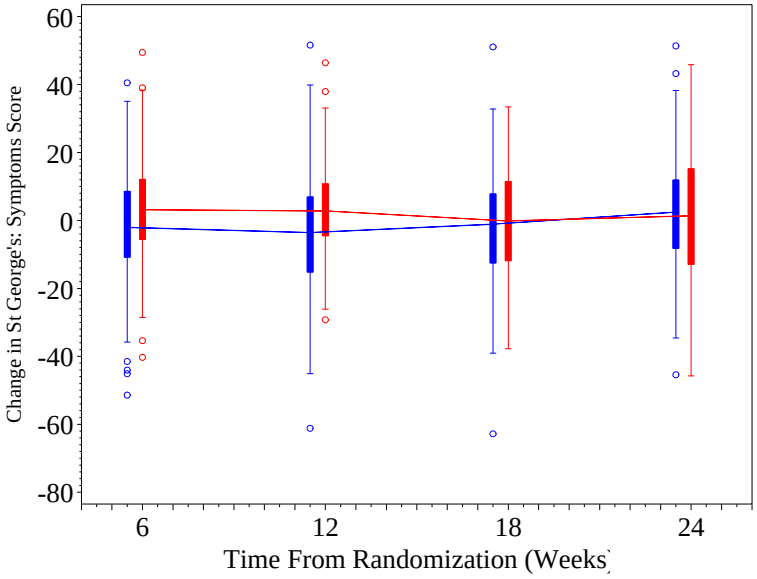

40
20
0
-20
-40
-60
Change in A-a Gradient (mmHg)
6
12
18
24
Time From Randomization (Weeks)

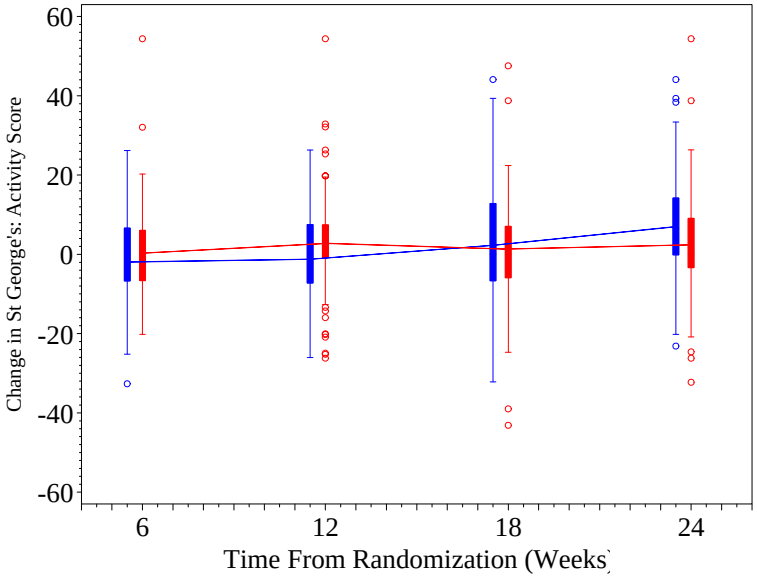

20
10
0
-10
-20
-30
Change in SaO2 (%)
6
12
18
24
Time From Randomization (Weeks)

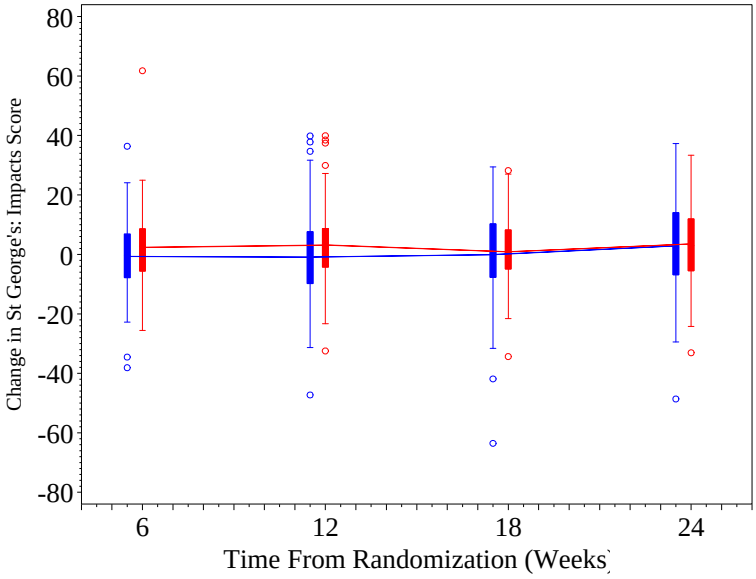

100
80
60
40
20
0
-20
-40
-60
Change in UCSD SoB Questionnaire Total
6
12
18
24
Time From Randomization (Weeks)

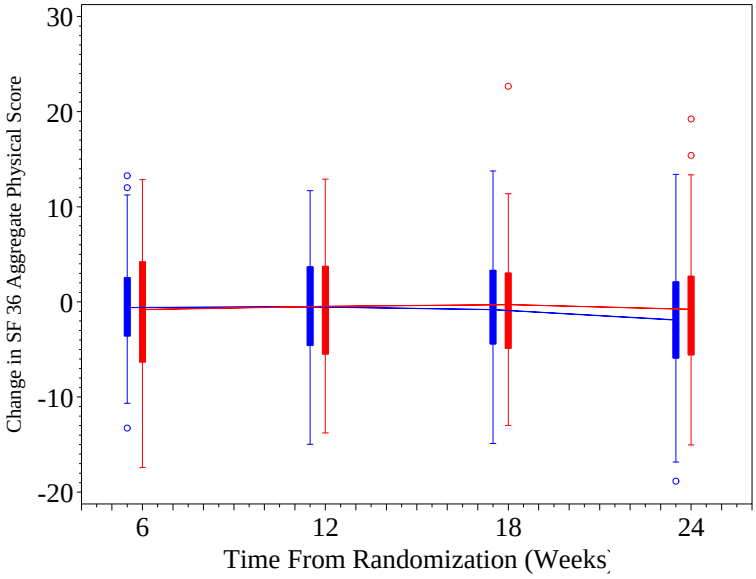

12
8
4
0
-4
-8
Change in Borg Scale Post-Walk Rating
6
12
18
24
Time From Randomization (Weeks)

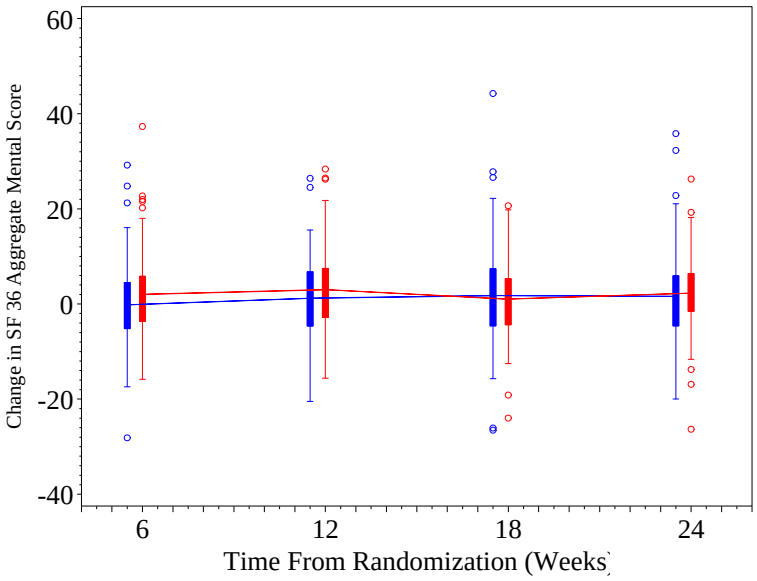

60
40
20
0
-20
-40
-60
Change in St George's: Total Score
6
12
18
24
Time From Randomization (Weeks)

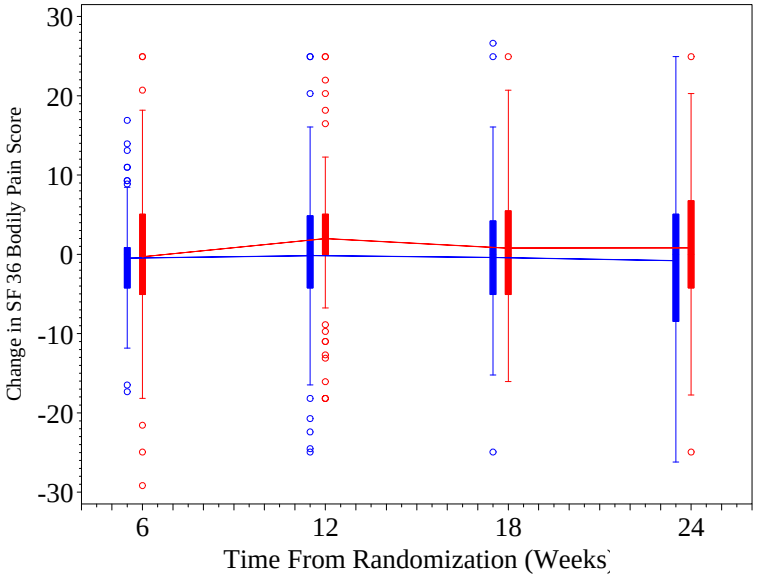

60
40
20
0
-20
-40
-60
-80
Change in St George's: Symptoms Score
6
12
18
24
Time From Randomization (Weeks)

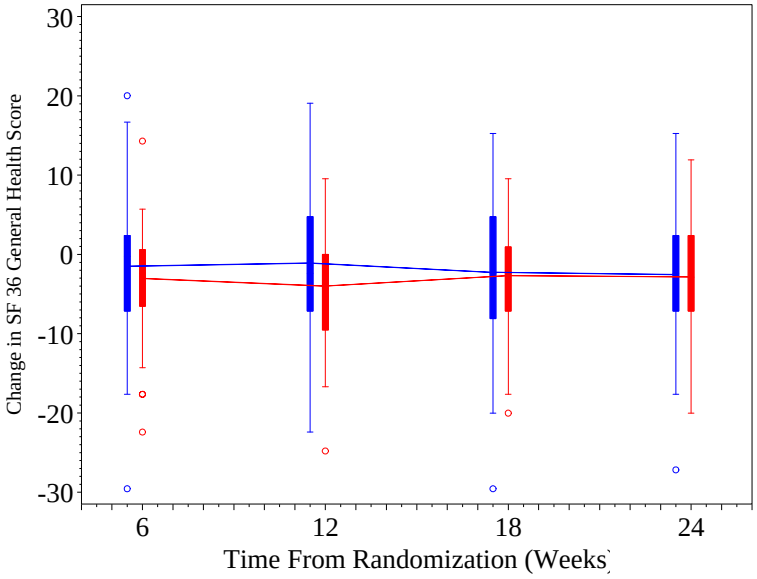

60
40
20
0
-20
-40
-60
Change in St George's: Activity Score
6
12
18
24
Time From Randomization (Weeks)

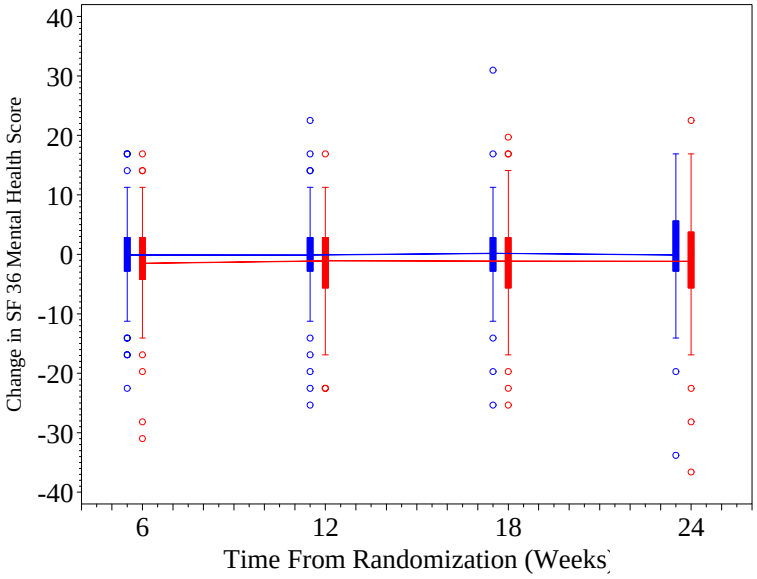

80
60
40
20
0
-20
-40
-60
-80
Change in St George's: Impacts Score
6
12
18
24
Time From Randomization (Weeks)

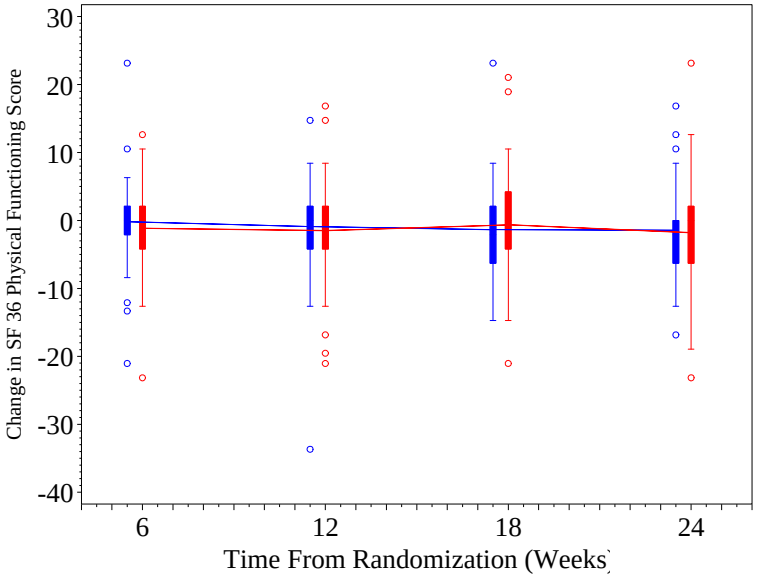

30
20
10
0
-10
-20
Change in SF 36 Aggregate Physical Score
6
12
18
24
Time From Randomization (Weeks)

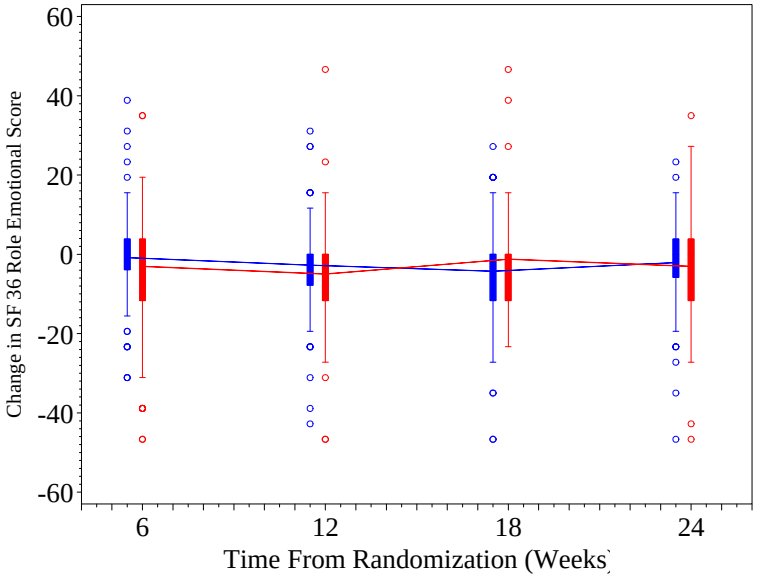

60
40
20
0
-20
-40
Change in SF 36 Aggregate Mental Score
6
12
18
24
Time From Randomization (Weeks)

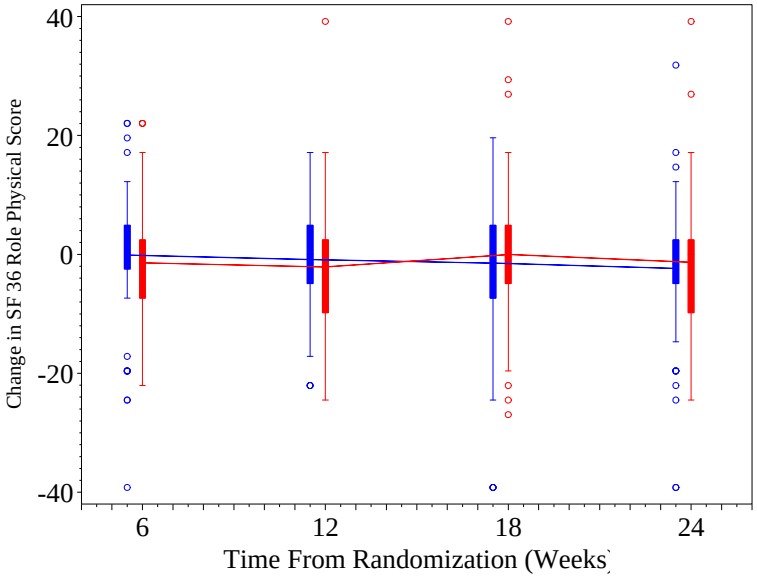

30
20
10
0
-10
-20
-30
Change in SF 36 Bodily Pain Score
6
12
18
24
Time From Randomization (Weeks)

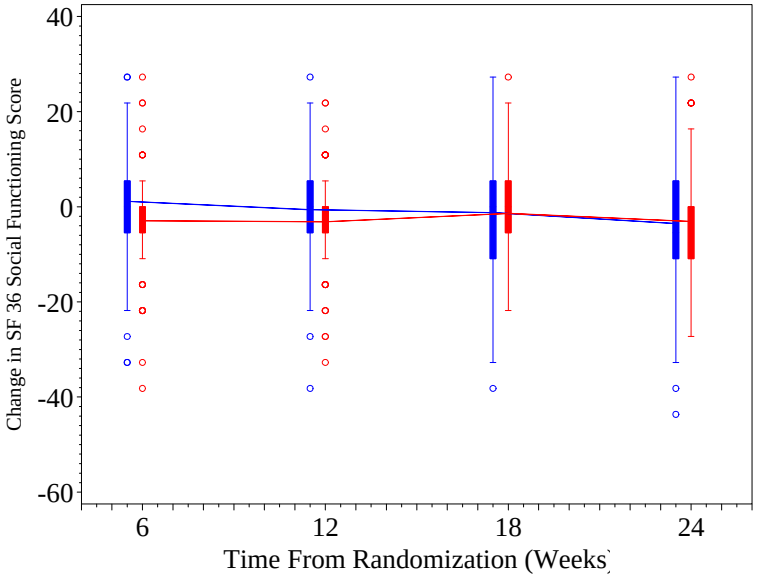

Change in SF 36 General Health Score
30
20
10
0
-10
-20
-30
6
12
18
24
Time From Randomization (Weeks)

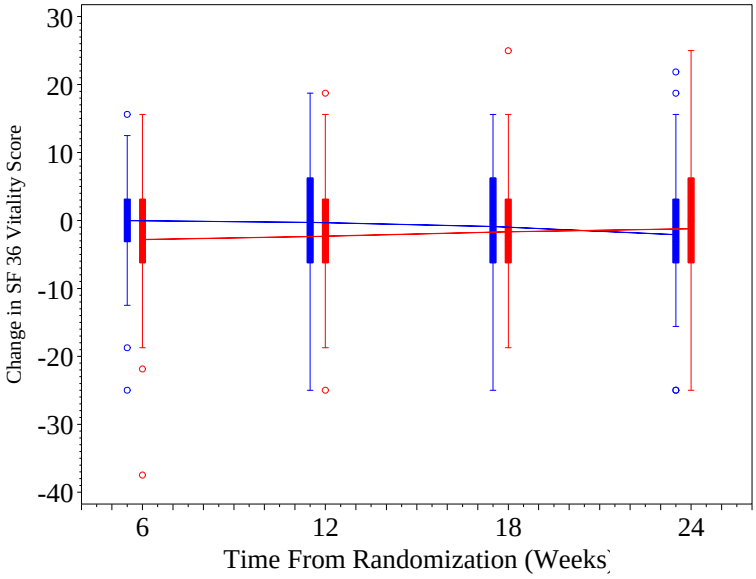

Change in SF 36 Mental Health Score
40
30
20
10
0
-10
-20
-30
-40
6
12
18
24
Time From Randomization (Weeks)

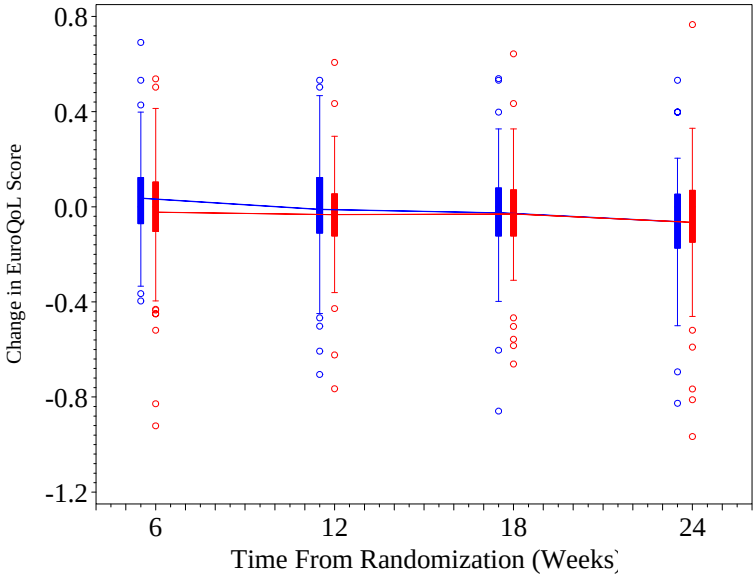

Change in SF 36 Physical Functioning Score
30
20
10
0
-10
-20
-30
-40
6
12
18
24
Time From Randomization (Weeks)

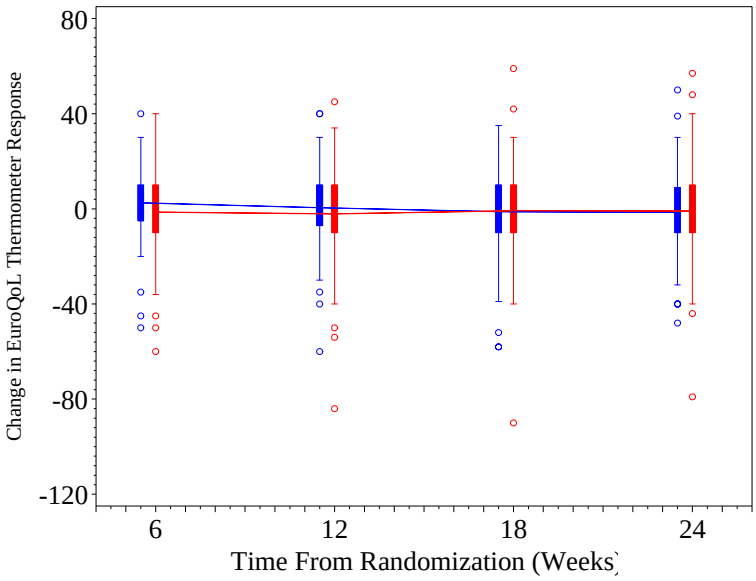

Change in SF 36 Role Emotional Score
60
40
20
0
-20
-40
-60
6
12
18
24
Time From Randomization (Weeks)


40
20
0
-20
-40
Change in SF 36 Role Physical Score
6
12
18
24
Time From Randomization (Weeks)


40
20
0
-20
-40
-60
Change in SF 36 Social Functioning Score
6
12
18
24
Time From Randomization (Weeks)


30
20
10
0
-10
-20
-30
-40
Change in SF 36 Vitality Score
6
12
18
24
Time From Randomization (Weeks)

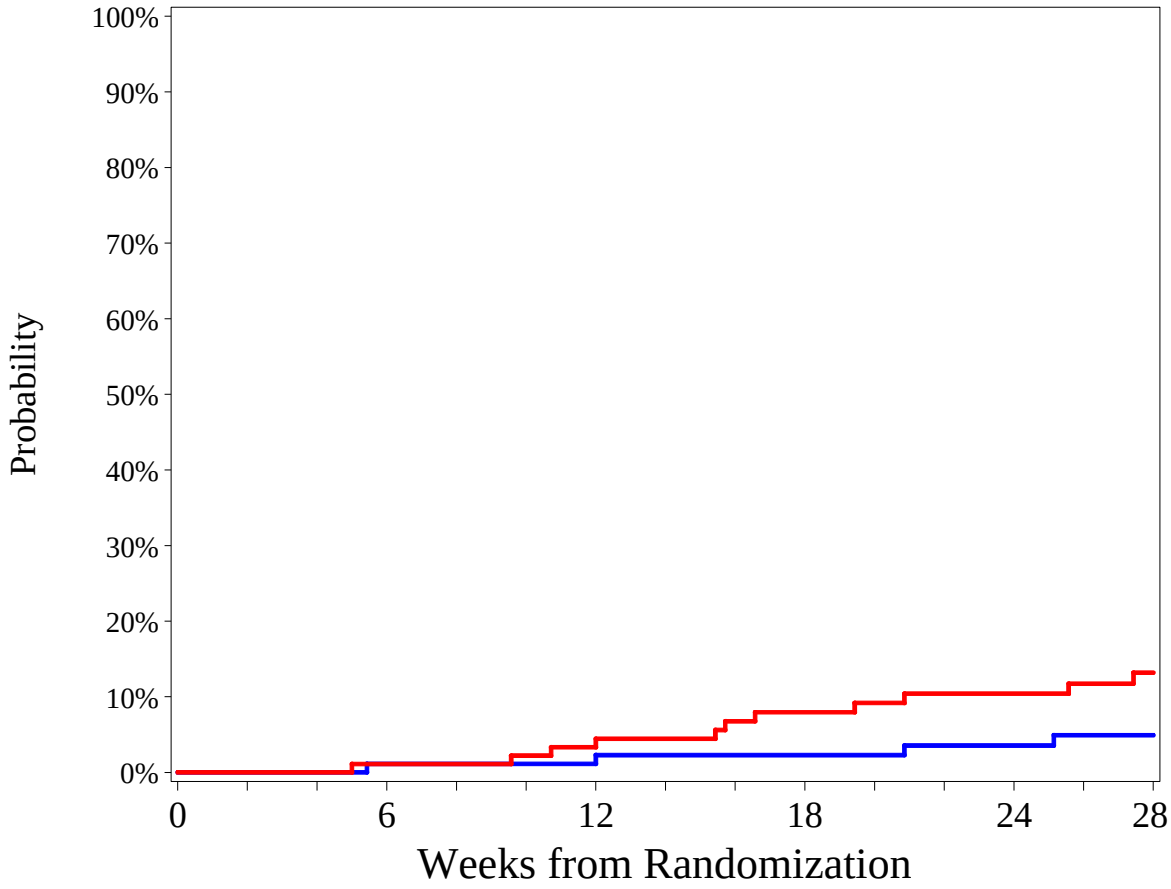

0.8
0.4
0.0
-0.4
-0.8
-1.2
Change in EuroQoL Score
6
12
18
24
Time From Randomization (Weeks)


80
40
0
-40
-80
-120
Change in EuroQoL Thermometer Response
6
12
18
24
Time From Randomization (Weeks)

Section F: Mortality Curves

Blue: Sildenafil / Sildenafil **Red: Placebo / Sildenafil**

Sildenafil / Sildenafil number at risk : baseline – 89, 6-weeks 87, 12-weeks 84, 18-weeks 78, 24-weeks 73, 28-weeks 57.
Placebo / Sildenafil number at risk : baseline – 91, 6-weeks 90, 12-weeks 85, 18-weeks 77, 24-weeks 71, 28-weeks 50.
Log-rank test to 12 weeks p-value=0.43
Log-rank test to 24 weeks p-value=0.08
Log-rank test to 28 weeks p-value=0.07



Section G: 6-Minute Walk Test Protocol

The IPFnet procedure for performing 6MWT was based on the 2005 ATS guidelines.

Introduction

The 6MWT is a simple test designed to test a subject's exercise capacity while performing an everyday activity. It has the advantage of not requiring complicated exercise equipment, specialized technicians, and the ability to evaluate the integrated response of the cardiac, pulmonary, and muscular systems related to exercise. It does not provide specific system information related to which system(s) is responsible for limitation. Change in 6MWT distance is a standard, accepted measure of drug efficacy in studies of pulmonary arterial hypertension; however, less is known about its use as a measure in idiopathic pulmonary fibrosis where desaturation has been shown to be a more robust predictor of subsequent mortality. This procedure combines the recommendations from the ATS guidelines for the 6MWT as well as experience from published trials and recent studies of IPF.

1. The screening 6MWT was performed to determine oxygen requirements for all subsequent tests and to make sure a walk distance of at least 50 meters was achieved.
2. Two 6MWTs were performed at the enrollment visit with at least one hour of rest between testing. The six minute walk distance for these enrollment walks had to be within 15% of each other or the subject was not included in the study.
3. The 15% difference was calculated by taking the absolute value of the difference between the two distances and dividing it by the larger of the two walk distances (e.g. the difference between a walk of 85 meters and a walk of 100 meters was determined by taking the difference between the two (15 meters) and dividing by the larger of the two (100 meters). So 15/100 = 15%, and these walks would not exclude the subject.)
4. There were no more than two 6MWTs administered during the enrollment visit. If one of the walks in the judgment of the investigator was not satisfactory due to unusual circumstances (equipment failure, subject stumbling, etc.), then that walk was nullified before completion and the subject was eligible to perform another walk (with at least one hour between the walks.)
5. The higher of the two distances was used as the enrollment value for subsequent comparisons.

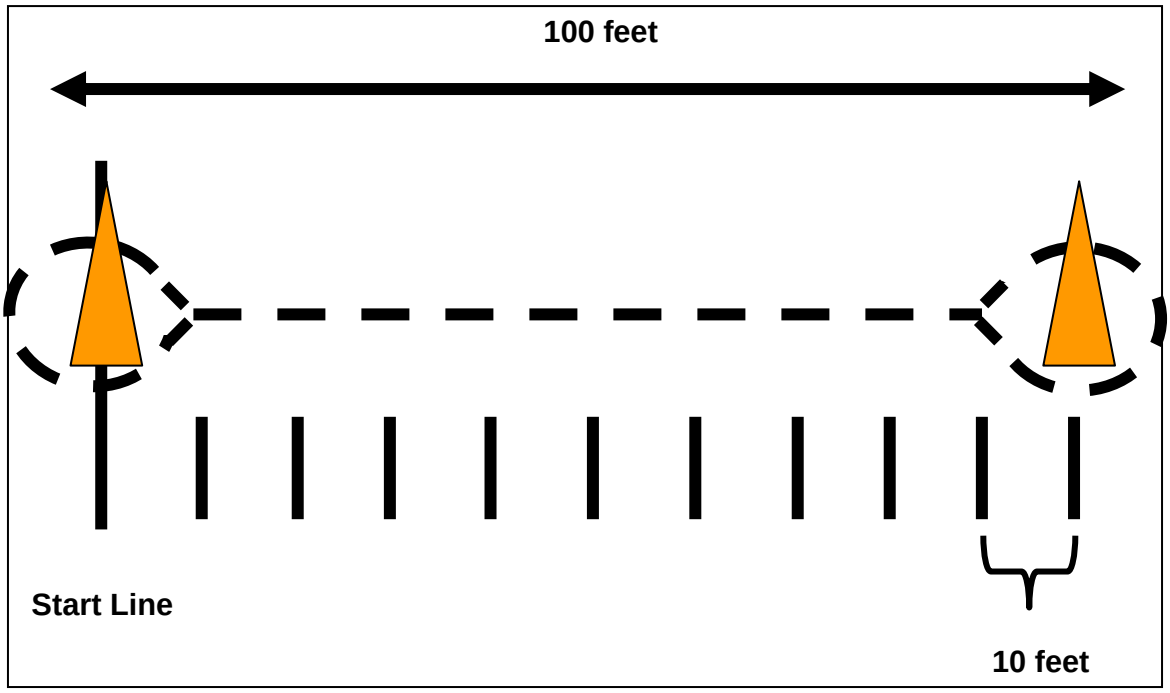
6. A single 6MWT was performed on all subsequent visits after enrollment.

Technical Aspects

The location of the 6MWT was of adequate length and width, climate controlled, and rarely traveled by other individuals The subject was able to walk without having his or her stride or momentum interrupted by frequent turning or other interruptions/distractions. Specifications are:

1. The ideal walking course was at least 100 feet in length. If space was an issue, the course could be 50 feet or 75 feet; however, the length of the course was consistent throughout the study.
2. The walking surface was consistent with each test. (Note: If the 6MWT is conducted on a carpeted surface for the first test, then it was consistent throughout the study)
3. A starting line marked the beginning of the track and tape was placed every 10 feet along the course
4. Turn-around points were marked with a cone (see **Figure E1.**)
5. The same location was used for each subject

Figure E1. **6MWT Turn-Around Points**



Required Equipment

1. Countdown timer (or stopwatch)
2. Mechanical lap counter
3. Two small cones to mark the turnaround points
4. Worksheets on a clipboard (provided by IPFnet)
5. A source of oxygen
6. Sphygmomanometer
7. Emergency equipment
8. Pulse Oximeter

Safety Issues

Emergency equipment ("crash cart") and personnel were immediately available. The technician was trained in basic life support. Additional supplies included:

a. A telephone to call for help
b. Oxygen
c. Sublingual nitroglycerin
d. Aspirin
e. Albuterol

Contraindications for testing included:

a. Unstable angina during the previous 30 days
b. Myocardial infarction during the previous 30 days
c. Unstable vital signs including heart rate > 120, systolic blood pressure less than 90mmHg or greater than 180mmHg, diastolic blood pressure greater than 100mmHg
d. If the technician suspects that it is unsafe for the subject to undergo testing they will contact the clinical centers principal investigator who will assess if the subject is able to undergo testing.

Reasons to stop the test prior to completion included:

a. Pulse oximetry (SpO_2) dropped to below 80% for six consecutive seconds
b. Chest pain
c. Intolerable dyspnea

d. Leg cramps
e. Staggering
f. Diaphoresis
g. Pale, ashen, or unstable appearance of the subject

Performance of the test

Subject Preparation

a. Comfortable clothing should be worn
b. Appropriate shoes for walking should be worn
c. Walking aids (cane, walker, etc.) should be utilized
d. Subject should be on their usual medical regimen (inhalers, etc.)
e. A light meal is acceptable prior to testing
f. Subjects should not have exercised vigorously for 2 hours prior to testing
g. Subjects must rest at least 10 minutes prior to the start of the test and one hour between the first and second tests on the enrollment visit
h. The technician explains the purpose of the equipment (timer, pulse oximeter).
i. The technician explains the walk course by reading the standard text below and demonstrates how to walk around the cones:

"The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

"You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."

Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.

"Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this

starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog. Start now, or whenever you are ready."

Resting oxygen titration

The goal of oxygen titration was to determine at the enrollment the baseline oxygen flow rate for all subsequent walk tests during the study. The subject was seated and resting for at least 10 minutes. Pulse oximetry was checked and recorded. Subjects of resting saturation of 88% or greater performed the walk on room air. If the SpO_2 was less than 88%, 2 liters of supplemental oxygen were provided and the SpO_2 was rechecked and recorded after 10 minutes. This titration was repeated at 4 and 6 liters until a resting $SpO_2 \geq 92\%$ was achieved. If a subjects SpO_2 remained < 92% with 6 liters of supplemental oxygen the subject was not eligible for the study. The amount of oxygen required to obtain a resting $SpO_2 \geq 92\%$ at baseline is the amount that was used for each subsequent test in the study.

If subject was using a level of supplemental oxygen greater than the level of oxygen set at enrollment, that subject was put on enrollment level of oxygen for 20 minutes prior to beginning the test. If a subject was unable to reach a resting $SpO_2 \geq 88\%$ on the prior enrollment level of supplemental oxygen, the subject was not walked and a 0 was recorded for that test.

Six-minute walk test procedure

a. Connect the pulse oximeter to the subject and insure a good signal. Confirm that the heart rate registered by the oximeter matches a manually obtained radial heart rate. Clip the oximeter cable to the subjects clothing to avoid tension

b. The subject should complete the pre-walk Borg scale

c. The technician should carry/push all equipment for the subject (clipboard, oximeter, supplemental oxygen system).

d. The technician should walk behind the subject at all times and not talk to anyone else except the subject. The technician should only use the following phrases of encouragement during the test. The technician should not use any other body language

1) After the first minute: "You are doing well. You have 5 minutes to go."

2) After the 2nd minute: "You are doing well. You have 4 minutes to go."
3) After the 3rd minute: "You are doing well. You are halfway done"
4) After the 4th minute: "You are doing well. You have 2 minutes to go."
5) After the 5th minute: "You are doing well. You only have 1 minute to go."
6) With 15 seconds to go: "In a moment I'm going to tell you to stop. When I do just stop right where you are and I will come to you."

e. The end-of-walk Borg scale should be completed at the end of the test

f. The technician should congratulate the subject on good effort and offer a drink of water

Termination of the test

The test was terminated when any of the following occur:

a. Six minutes are up

b. SpO2 drops below 80% for 6 consecutive seconds.

c. Subject develops signs or symptoms requiring test termination

Data collection

The following data were captured:

a. Date & time of test

b. Flow rate of oxygen used during test

c. At baseline, during each minute of the test, and for each of three minutes of recovery the technician should record SpO_2 and heart rate

d. Duration of test in minutes and seconds

e. Reason for stopping if test was terminated prior to 6 minutes

f. Distance walked

Immediately after the walk test, the tester will obtain a rating of dyspnea using the Borg scale:

Perceived Breathlessness (Borg Scale)

0	**NOTHING AT ALL**
	VERY VERY SLIGHT (just noticeable)
1	**VERY SLIGHT**
2	**SLIGHT**
3	**MODERATE**
4	**SOMEWHAT SEVERE**
5	**SEVERE**
6	
7	**VERY SEVERE**
8	
9	**VERY VERY SEVERE (almost maximum)**
10	**MAXIMUM**

STEP-IPF

SILDENAFIL TRIAL OF EXERCISE PERFORMANCE IN IDIOPATHIC PULMONARY FIBROSIS

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

Version 6.2

March 30, 2007

Amendment 1 October 31, 2007

Amendment 2 April 15, 2008

Compiled by:

The IPFnet STEP Protocol Committee

Distributed by:

The IPFnet Coordinating Center

Duke Clinical Research Institute

Duke University

PO Box 17969

Durham, NC 27715

Protocol Summary

PRODUCT	Revatio® (sildenafil citrate)
CLINICALTRIALS.GOV IDENTIFIER	NCT00517933
PROTOCOL TITLE	Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Confirmed idiopathic pulmonary fibrosis and a diffusing capacity of the lung < 35% of predicted
STUDY OBJECTIVES	To demonstrate improved 6-minute walk test distance in subjects with advanced idiopathic pulmonary fibrosis treated for 12 weeks with sildenafil compared with placebo. To demonstrate improved dyspnea and quality of life in subjects with advanced idiopathic pulmonary fibrosis treated for 12 weeks with sildenafil compared with placebo.
STUDY DESIGN	Multi-center, randomized, double-blind, placebo-controlled period, followed by open-label period
TREATMENT REGIMEN	20 mg of sildenafil or placebo 3 times a day, daily for 12 weeks, then 20 mg of sildenafil 3 times a day, daily for 12 weeks
ROUTE OF ADMINISTRATION	Oral
INTERVAL BETWEEN FIRST AND LAST DOSES OF ACTIVE STUDY AGENT	24 weeks
DURATION OF STUDY PARTICIPATION	24 weeks
END OF STUDY DEFINITION	24 weeks + 28 days after final subject enrollment
NUMBER OF SUBJECTS	170 (1:1)
NUMBER OF SITES	At least 12
PRIMARY ENDPOINT	Change in 6-minute walk distance from enrollment to week 12 (dichotomized as ≥ 20% improvement or < 20% improvement)
SECONDARY ENDPOINTS	Change in 6-minute walk distance from enrollment to weeks 6 and 12 Change in quality of life from enrollment to weeks 6 and 12 Change in New York Heart Association class from enrollment to weeks 6 and 12 Change in dyspnea using Borg scale from enrollment to weeks 6 and 12 Change in dyspnea using University of California at San Diego

	Shortness of Breath Questionnaire from enrollment to weeks 6 and 12 Change in oxygen desaturation measures (time, distance, recovery time) during 6-minute walk test from enrollment to weeks 6 and 12 Change in forced vital capacity and diffusing capacity of the lung from enrollment to weeks 6 and 12 Change in resting partial pressure of arterial oxygen (PaO_2), oxygen saturation measured using pulse oximetry (SpO_2), arterial oxygen saturation (SaO_2), and alveolar-arterial (A-a) gradient from enrollment to week 12 Change in brain natriuretic peptide level from enrollment to weeks 6 and 12 Acute exacerbation of idiopathic pulmonary fibrosis Number of all-cause hospitalizations Survival time
Second Period Endpoints (open-label phase)	Changes in 6MWD from enrollment to week 24 Changes in QOL from enrollment to week 24 Change in NYHA class from enrollment to week 24 Changes in dyspnea using Borg scale from enrollment to week 24 Changes in dyspnea using UCSD SOBQ from enrollment to week 24 Changes in O_2 desaturation measures (time, distance, recovery time) during 6MWT from enrollment to week 24 Changes in FVC, DLco from enrollment to week 24 Changes from enrollment in resting PaO_2, SpO_2, SaO_2, and A-a gradient from enrollment to week 24 Changes in BNP level from enrollment to week 24 AEx of IPF Number of all-cause hospitalizations Survival time
INTERIM ANALYSIS	One planned interim analysis at 0.50 information time

Study Sponsor: **National Heart Lung and Blood Institute, NIH**

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List of Abbreviations

6MWD	6-minute walk distance
6MWT	6-minute walk test
A-aPO_2	alveolar-arterial partial pressure of oxygen
ABG	arterial blood gas
AE	adverse event
AEx	acute exacerbation
ALT	alanine aminotransferase
AS	aortic stenosis
AST	aspartate aminotransferase
AV	atrioventricular
BAL	bronchoalveolar lavage
BDS	Borg dyspnea scale
BNP	brain natriuretic peptide
BUN	blood urea nitrogen
CRF	case report form
CT	computed tomography
DBP	diastolic blood pressure
DCC	Data Coordinating Center
DCF	data clarification form
DL_{CO}	diffusing capacity of the lung for carbon monoxide
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
EF	ejection fraction
FDA	Food and Drug Administration
FVC	forced vital capacity
GCP	Good Clinical Practice
GMP	guanosine monophosphate
HHS	Health & Human Services (U.S. Dept . of)
HIPAA	Health Insurance Portability and Accountability Act

HRCT	high-resolution computed tomography
IFN γ-1b	interferon gamma-1b
IHSS	idiopathic hypertrophic subaortic stenosis
IIR	investigator initiated research
ILD	interstitial lung disease
IPF	idiopathic pulmonary fibrosis
IPFnet	Idiopathic Pulmonary Fibrosis Clinical Research Network
IRB	institutional review board
IVRS	interactive voice response system
MI	myocardial infarction
MOOP	Manual of Operating Procedures
mPAP	mean pulmonary artery pressure
NAION	nonarteritic ischemic optic neuropathy
NHLBI	National Heart Lung and Blood Institute
NIH	National Institutes of Health (U.S.)
NPV	negative predictive value
NSIP	nonspecific interstitial pneumonia
NYHA	New York Heart Association
PA	arterial pressure
PaO_2	partial pressure of arterial oxygen
PAP	pulmonary artery pressure
PFT	pulmonary function test
PH	pulmonary hypertension
PHS	Public Health Service (U.S.)
PI	principal investigator
PH	pulmonary hypertension
PPV	positive predictive value
RHC	right-heart catheterization
QOL	quality of life
RVSP	right ventricular systolic pressure
SAE	serious adverse event
SaO_2	oxygen saturation

SAP	statistical analysis plan
SBP	systolic blood pressure
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvate transaminase
SpO_2	oxygen saturation measured using pulse oximetry
STEP-IPF	SILDENAFIL TRIAL OF EXERCISE PERFORMANCE IN IDIOPATHIC PULMONARY FIBROSIS
TIA	transient ischemic attack
t.i.d.	three times a day
UCSD SOBQ	University of California at San Diego Shortness of Breath Questionnaire
UIP	usual interstitial pneumonia
WHO	World Health Organization

A STUDY OF SILDENAFIL IN IDIOPATHIC PULMONARY FIBROSIS

1. SUMMARY

This protocol proposes to test the following hypothesis: Treatment with sildenafil will improve exercise capacity and quality of life (QOL) in subjects with advanced idiopathic pulmonary fibrosis (IPF). This study will be a 2-period study, with treatment and evaluation lasting a total of 24 weeks. To address the primary hypothesis of this protocol, we propose a 12-week randomized, double-blind, placebo-controlled trial of sildenafil in 170 subjects with advanced IPF (defined as diffusing capacity of the lung for carbon monoxide [DLco] < 35% predicted). The primary endpoint of this trial is change in 6-minute walk distance (6MWD) over 12 weeks. The second study period will be used to estimate the 24-week safety and efficacy profile of sildenafil therapy. Secondary endpoints will include change in dyspnea and QOL. This clinical trial will be performed as part of the National Institutes of Health (NIH)/National Heart Lung and Blood Institute (NHLBI)-sponsored Idiopathic Pulmonary Fibrosis Clinical Research Network (IPFnet).

2. HYPOTHESIS AND SPECIFIC AIMS

2.1. Study Hypothesis

Treatment with sildenafil will improve exercise capacity and QOL in subjects with advanced IPF.

2.2. Specific Aim 1

To demonstrate improved 6-minute walk test (6MWT) distance in subjects with advanced IPF treated for 12 weeks with sildenafil compared with placebo.

2.3. Specific Aim 2

To demonstrate improved dyspnea and QOL in subjects with advanced IPF treated for 12 weeks with sildenafil compared with placebo.

3. BACKGROUND AND SIGNIFICANCE

3.1. Pulmonary Hypertension is Common in Advanced Idiopathic Pulmonary Fibrosis

Secondary pulmonary hypertension (PH) is common in people with advanced IPF, which is generally defined by severely reduced lung volumes and diffusing capacity (< 35%). IPF is associated with aberrant vascular remodeling (Turner-Warwick 1963; Keane et al. 1999; Cosgrove et al. 2004), a phenomenon that likely contributes to this association. Historical data have suggested the majority of people with IPF have PH. In a cohort of 31 IPF subjects, PH at rest (arterial pressure [PA] mean > 20 mm Hg) was reported in 55% of subjects. In this cohort, 80% of IPF subjects had PH with exercise (PA mean > 30 mm Hg) (Weitzenblum et al. 1983). In 70% of subjects with advanced pulmonary fibrosis, an auscultatory finding of a loud pulmonary second sound consistent with PH was present, and thickened muscular pulmonary arteries with medial hypertrophy and fibrous intimal proliferation were reported (Stack, Choo-King, and Heard 1972; Crystal et al. 1976). Subjects with IPF had higher pulmonary artery pressures and lower cardiac indices both at rest and with exercise than subjects with other forms of interstitial lung disease (ILD) (Weitzenblum et al. 1983).

Recent data from the field of lung transplantation have corroborated these early data. In one large study of subjects with ILD undergoing formal evaluation for lung transplantation, the prevalence of PH at rest assessed by right-heart catheterization (RHC) was found to be 59% of 106 subjects (Arcasoy et al. 2003). In a second large study of 79 IPF subjects undergoing pretransplantation RHC, the prevalence of PH at rest was 32% (Lettieri et al. 2006).

3.2. Pulmonary Hypertension in Advanced Idiopathic Pulmonary Fibrosis Shortens Survival

The presence of PH in advanced IPF has a significant adverse impact on survival. An echocardiographic systolic pulmonary artery pressure of greater than 50 mm Hg was associated with a median survival time of 0.7 years in subjects with well-documented IPF (Nadrous et al. 2005). In a large study of subjects with advanced IPF, the 1-year mortality rate was higher among those with PH (28.0% vs. 5.5%, p=0.002) (Lettieri et al. 2006). Over the entire study period this translated to an odds ratio for mortality of 2.6 (95% CI: 2.3-3.1). A second study reported on 88 subjects with ILD (the majority had IPF) and showed that the

presence of severe PH (defined as mean pulmonary artery pressure [mPAP] ≥ 35 mm Hg) was predictive of higher mortality (43% vs. 15% mortality over a mean of 10 months, $p < 0.05$) (Leuchte et al. 2004).

3.3. Sildenafil May Improve Pulmonary Hypertension and Exercise Tolerance in Advanced Idiopathic Pulmonary Fibrosis

PH associated with advanced IPF is a potentially treatable condition (Arcasoy et al. 2003). Pulmonary-selective vasodilators have been suggested for the treatment of PH secondary to fibrotic lung disease such as IPF (Olschewski et al. 1999; Ghofrani et al. 2002; Runo and Loyd 2003). Sildenafil is a phosphodiesterase-5 inhibitor that stabilizes the second messenger of nitric oxide, cyclic guanosine monophosphate (GMP). Phosphodiesterases are a superfamily of enzymes that inactivate cyclic adenosine monophosphate and cyclic GMP with different tissue distribution and substrate specificities (Beavo 1995). Phosphodiesterase-5 is abundantly expressed in lung tissue (Ahn et al. 1991; Peao et al. 1994), and results of studies performed in subjects with primary pulmonary hypertension (PPH) suggest that sildenafil causes pulmonary vasodilatation, even in the absence of exogenous nitric oxide administration (Wilkens et al. 2001; Ghofrani et al. 2002).

In a randomized, controlled, open-label trial of 16 individuals with PH secondary to pulmonary fibrosis (the underlying diseases with subject numbers were: IPF - 7, CREST syndrome - 3, systemic sclerosis - 2, silicosis - 2, or extrinsic allergic alveolitis - 2), sildenafil showed significant effects on pulmonary vascular resistance (Ghofrani et al. 2002). After inhalation of nitric oxide, subjects were randomized to either maximum tolerated dose of intravenous epoprostenol (mean 8.0 ng/kg per min; n=8) or oral sildenafil (50 mg; n=8). Their primary objective was to assess pulmonary vasodilatory potency of sildenafil by comparison with inhaled nitric oxide and infused epoprostenol. A single dose of sildenafil (50 mg) reduced pulmonary vascular resistance by nearly one-third and increased the mean arterial blood oxygen tension by 14 mm Hg. The vasodilatory response to 50 mg of sildenafil began within 15 minutes and reached a plateau after 45 to 60 minutes. The drug was well tolerated with no adverse effects on ventilation-perfusion matching. In contrast with infused epoprostenol, sildenafil showed selectivity for well-ventilated areas of the lung, resulting in improvement rather than deterioration in gas exchange.

3.4. Sildenafil Safety Data in Subjects with Advanced Lung Disease

Sildenafil appears to be a generally well-tolerated drug in subjects with advanced disease. Only 1 of 14 subjects studied at the University of California at Los Angeles (UCLA) (see section 4.1 below) had a significant adverse event (AE) (transient hypotension), requiring sildenafil to be stopped. A second pilot study of sildenafil reported on 3 subjects with IPF, and none had significant AEs (Madden and Crerar-Gilbert 2005). In a large trial of sildenafil for PPH, 160 subjects had World Health Organization (WHO) class III disease and 9 had WHO class IV disease (Galie et al. 2005). Over 12 weeks, there were 2 serious adverse events (SAEs) related to sildenafil and 4 withdrawals due to side effects in the entire study cohort.

3.5. Brain Natriuretic Peptide and Gas Exchange May Be Reasonable Surrogate Markers of Pulmonary Hypertension in Idiopathic Pulmonary Fibrosis

RHC is the gold standard for diagnosis of PH in people with advanced IPF (Arcasoy et al. 2003; Runo and Loyd 2003). However, it is an expensive and invasive method with substantial risks for complications. It is also a highly technical procedure; properly performed RHC is of limited availability in the community. Reliable, noninvasive approaches to the diagnosis of PH in advanced IPF would improve subject safety, cost, and accessibility to accurate diagnostic tools for community physicians.

Echocardiography is not an accurate predictor

Doppler echocardiography is commonly used to estimate systolic pulmonary artery pressure (PAP) and to diagnose PH; however, estimation of systolic PAP by echocardiography is frequently inaccurate in people with ILD. In a cohort study of 374 lung-transplant candidates, the performance characteristics of echocardiography compared with RHC in the determination of systolic PAP and diagnosis of PH were investigated (Arcasoy et al. 2003). Estimation of systolic PAP by echocardiography was possible in 166 subjects (44%). The correlation between systolic PAP estimated by echocardiography and measured by cardiac catheterization was good ($r = 0.69$, $p < 0.001$). However, 52% of pressure estimations were found to be inaccurate (> 10 mm Hg difference compared with measured pressure), and 48% of subjects were misclassified as having PH when estimated by echocardiography. Systolic

PAP estimation predicted PH in subjects with ILD with 85% sensitivity, 17% specificity, 60% positive predictive value, and 44% negative predictive value. In light of the poor positive and negative predictive values of echocardiographic-estimated systolic PAP, reliance on this noninvasive technique can potentially lead to inaccurate diagnosis of PH in patients with IPF.

Brain natriuretic peptide (BNP) appears to be an accurate predictor of moderate or severe PH in advanced IPF

BNP is predominately secreted by the cardiac ventricles (Mukoyama et al. 1991). In a recent study, investigators aimed to characterize the role of BNP in the assessment of PH in 39 individuals with advanced pulmonary fibrosis whose underlying diseases were IPF (n=28), pulmonary fibrosis due to connective tissue disease (n=3), sarcoidosis (n=4), and hypersensitivity pneumonitis (n=4) (Leuchte et al. 2004). In that study, subjects with pulmonary fibrosis and elevated BNP levels (n = 20) had significantly more severe PH (mean pulmonary arterial pressure [mPAP] 40.85 ± 3.2 mm Hg) during RHC than those with pulmonary fibrosis and normal BNP levels (n = 19) (mPAP 23.42 ± 1.44 mm Hg) ($p < 0.001$). Brain natriuretic peptide concentrations predicted moderate-to-severe PH (mPAP ≥ 35 mm Hg) with 100% sensitivity and high specificity (89%). The same group reported a larger cohort of subjects and found similar results. In a group of 176 subjects (55 of whom had IPF), an elevated BNP was associated with a positive predictive value of 73% and a negative predictive value of 92% (Leuchte et al. 2004).

Based on these important but limited data, BNP appears to be a useful marker for moderate-to-severe PH (mPAP ≥ 35 mm Hg) in advanced pulmonary fibrosis. The sensitivity of BNP to detect mild-to-moderate PH (mPAP of 26–34 mm Hg) is unknown. The use of elevated BNP as a surrogate marker for PH is attractive but requires further investigation before it can be routinely employed.

Abnormal gas exchange is an accurate predictor of PH in advanced IPF

It has been reported that when the DLco falls below 45% of predicted, PH at rest can be expected (Campbell and Harris 1981). In a retrospective analysis of 79 consecutive IPF subjects undergoing pretransplantation RHC, age, sex, forced vital capacity (FVC), and total

lung capacity did not differ among those with or without PH (Lettieri et al. 2006). Diffusing capacity, however, was significantly lower in those with PH (37.6 ± 11.3% predicted vs. 31.1 ± 10.1% predicted, p=0.04). The need for supplemental oxygen together with a DLco < 40% predicted identified the presence of PH with 65.0% sensitivity, 94.1% specificity, 86.7% positive predicted value, 82.1% negative predictive value, and 83.3% accuracy. Nonetheless, only 15.2% of the cohort had both a supplemental oxygen requirement and a DLco < 40% predicted, illustrating the limited sensitivity of criteria requiring evidence of desaturation.

4. PRELIMINARY STUDIES

4.1. Open-label Pilot Study of Sildenafil in Subjects with Idiopathic Pulmonary Fibrosis and Pulmonary Hypertension

Recently published data from UCLA demonstrate improvement in 6MWD in subjects with IPF treated with sildenafil (see Table 1) (Collard et al. 2007). Fourteen subjects with IPF (6 biopsy-proven) and documented PH by RHC (mPAP ≥ 25 mm Hg) or echocardiography (right ventricular systolic pressure ≥ 35 mm Hg) were enrolled in an open-label trial of sildenafil and underwent pre- and post-6MWTs. Over an average follow-up of 90 days, 3 of the 14 subjects were unable to complete the study. Two had side effects from sildenafil (diarrhea [1] and hypotension [1]) and 1 was unable to complete the follow-up 6MWT due to chest pains. In the remaining 11 subjects, 8 had an improvement of ≥ 20% in their 6MWDs, with a median improvement of 40%.

Table 1: Open-label Sildenafil Results

Subject	Dose (mg) Three times a day (*t.i.d.*)	Baseline walk distance (m)	Follow-up walk distance (m)	Change in walk distance (%)	Adverse Effects
1	50	40	60	50	None
2	50	60	100	67	None
3	50	382	374	-2	None
4	50	100	140	40	None
5	50	135	95	-30	None
6	20	55	100	82	None
7	20	75	90	20	Diarrhea and headaches
8	20	60	185	208	None
9	50	518	525	1	None
10	20	70	85	21	Headache
11	40	155	--	--	Chest pain during follow-up walk test
12	20	105	--	--	Diarrhea
13	25	250	--	--	Transient hypotension
14	40	65	270	315	Blurred vision

4.2. Long-term Treatment with Sildenafil for Idiopathic Pulmonary Fibrosis and Pulmonary Hypertension

Investigators at the University of the Saarland, Homburg, Germany, reported the effects of sildenafil during treatment for at least 3 months in 10 subjects with IPF and severe functional impairment (New York Heart Association [NYHA] classes III and IV) (Wilkens 2005). All subjects received a first dose of 25 mg sildenafil during vasoreactivity testing. Then all subjects were treated with sildenafil titrated to a dose of 3 x 50 mg/d. RHC during the initial oral dose of sildenafil showed a reduction in pulmonary vascular resistance of 28% (810 to

580 dyn sec cm-1). During a follow-up time of 8.4 months (range 4–18 months), significant improvements of gas exchange (increase in partial pressure of arterial oxygen [PaO_2] of 1.2 KPa [95% CI: -0.1, 2.5]), Borg dyspnea score, and QOL were achieved within the first month. No AEs with sildenafil treatment were noted.

4.3. Eight-week Open-label Pilot Study of Sildenafil for Idiopathic Pulmonary Fibrosis and Pulmonary Hypertension

A prospective open-label trial of 7 subjects with PH (3 with IPF) treated with 8 weeks of sildenafil showed a significant increase in 6MWT difference (pre-6MWD 80 meters and post 120 meters, $p = 0.03$) (Madden et al. 2006). All IPF subjects had improvement in their walk distances. The presence of PH was confirmed by RHC in all subjects (defined as mPAP $\geq$ 25 mm Hg). There were trends in improvement in pulmonary vascular resistance and mean PAP observed as well.

5. METHODS

5.1. Inclusion Criteria

Only subjects with a screening DLco (adjusted for hemoglobin) < 35% predicted and a diagnosis of IPF are eligible for this study. A diagnosis of IPF is defined in section 5.2. Elevation of the serum BNP level, while useful in identifying moderate-to-severe PH, is not a widely validated surrogate marker and is of unclear sensitivity and specificity in subjects with more moderate PH. Therefore, BNP will not be used as one of the inclusion criteria.

Subjects must be able to complete two consecutive pre-enrollment 6MWTs with distances within 15% of one another. Subjects will be walked at screening, to ensure ability to walk the minimum distance of 50m and to set the oxygen flow for future walks. At the enrollment visit, subjects will undergo two 6MWTs with a minimum of an hour's rest between the two. If the difference between the two distances is greater than 15%, the subject is not eligible for enrollment. If the distance of either walk is less than 50m, the subject is not eligible for enrollment.

5.2. Diagnosis of Idiopathic Pulmonary Fibrosis

Only subjects with definite IPF will be eligible for enrollment in this study. We will utilize a combination of clinical/physiologic features, high-resolution computed tomography (HRCT) and, if clinically indicated, surgical lung biopsy to establish the diagnosis of IPF. An algorithm for the diagnosis is provided to guide entry into the protocol as outlined in the inclusion and exclusion criteria (Figures 5.1 and 5.2). This multi-disciplinary approach uses expertise from clinicians, radiologists, and pathologists. Investigators at each site, in conjunction with central pathology, will work together to establish the diagnosis of IPF. This interactive approach to the diagnosis of IPF increases the level of agreement between observers (Flaherty et al. 2004).

A subject with suspected ILD should be evaluated for secondary causes including, but not limited to, environmental exposures, drugs, and systemic diseases. Presence of any of these findings felt to be significant enough to cause an ILD should disqualify the subject from entry into the trial.

If secondary causes are absent, an HRCT scan may be obtained. If an HRCT of sufficiently high quality has been obtained within the last 3 months, that scan may be used for diagnosis. In the appropriate clinical setting, the diagnosis of IPF can be made by the demonstration of a typical radiographic pattern on HRCT or by demonstration of usual interstitial pneumonia (UIP) pattern on a surgical lung biopsy. The following criteria for a radiographic (ie, nonsurgical) diagnosis will be used. **The presence of all major criteria <u>and</u> 3 of the 4 minor criteria are required to meet study criteria for the diagnosis of IPF.**

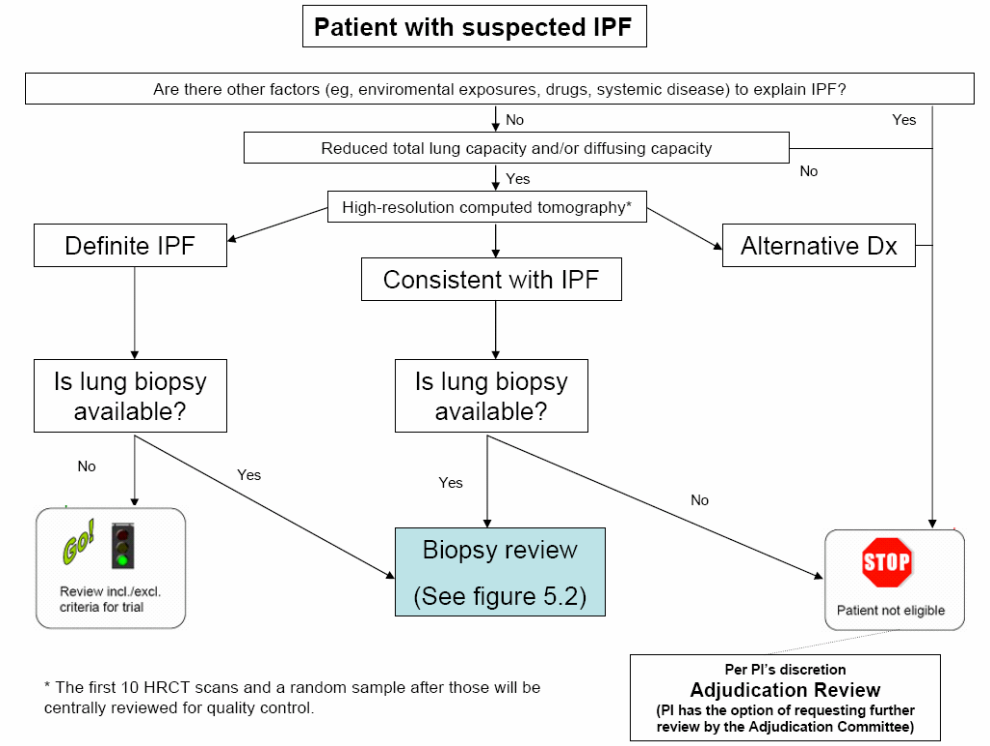

Figure 5.1: Radiological Diagnosis of Idiopathic Pulmonary Fibrosis

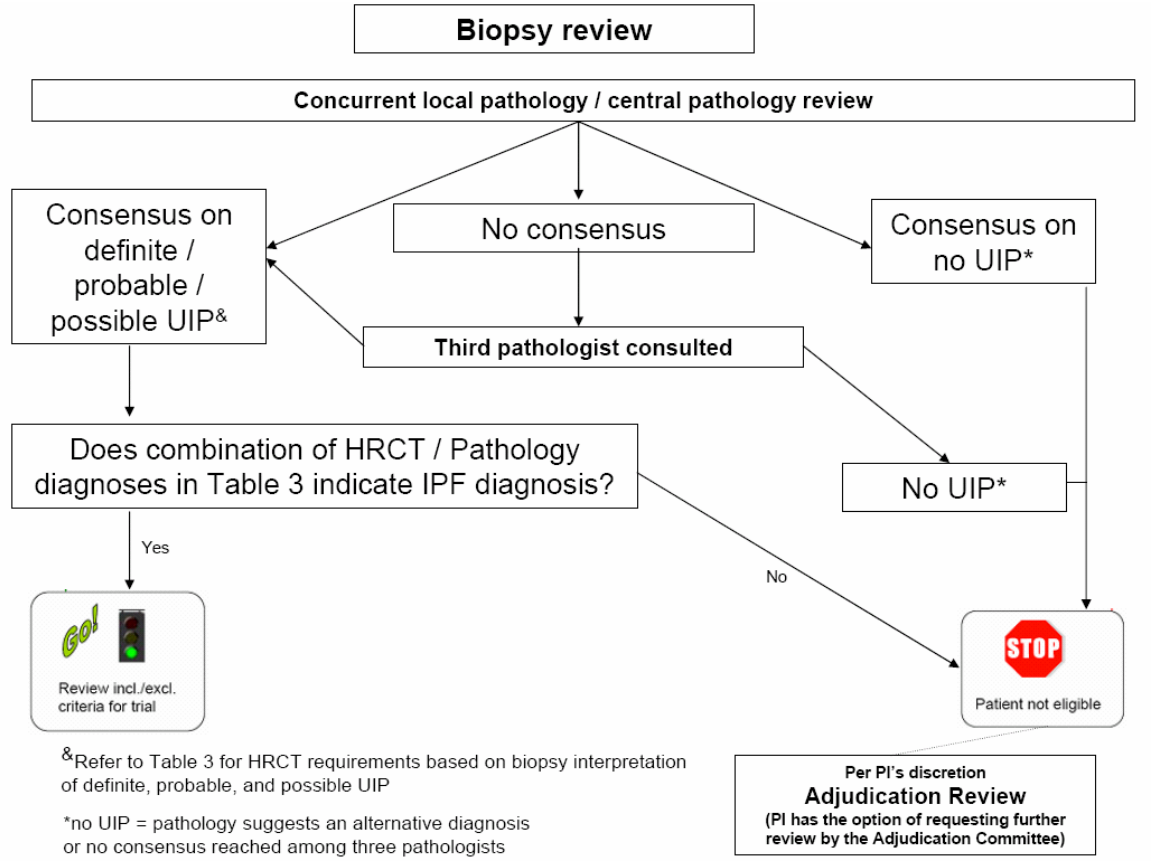

Figure 5.2: Pathological Diagnosis of Idiopathic Pulmonary Fibrosis

5.2.1. Major Criteria

1. **Clinical:** exclusion of other known causes (connective tissue diseases, environmental and drug exposures) of ILD

2. **Physiologic:** restriction on pulmonary function testing (PFT) and/or evidence of impaired gas exchange (decreased DL_{CO} or increased alveolar-arterial partial pressure of oxygen difference [A-aPO_2] at rest or with exercise)

3. **Radiographic:** HRCT with bibasilar reticular abnormality and honeycomb change with minimal ground glass opacities

5.2.2. Minor Criteria

1. Age > 50 years
2. Insidious onset of unexplained dyspnea
3. Duration of illness for ≥ 3 months
4. Bibasilar, inspiratory crackles

Unlike the American Thoracic Society/European Respiratory Society consensus criteria, bronchoscopy will not be required for diagnosis. This decision was made based on the experience of the IPFnet Steering Group members regarding the utility of bronchoscopy in the diagnosis of IPF. The presence of an atypical HRCT finding will require documentation of a definitive diagnosis by surgical lung biopsy.

We will not require central review of HRCT, as several studies have shown that a confident local interpretation of clinical/HRCT criteria as definite UIP is associated with a high positive predictive value for finding UIP at surgical lung biopsy (see Table 2). Differences in sensitivity in these series likely reflect subject selection as Flaherty et al. (Flaherty et al. 2003), evaluated only UIP and NSIP while Raghu et al. (Raghu et al. 1999) and Hunninghake et al. (Hunninghake et al. 2003) included a broader range of ILD.

Table 2: Operating Characteristics of Local HRCT Review for Diagnosis of Usual Interstitial Pneumonia

Researcher	**# of Subjects**	**Sensitivity** (%)	**Specificity** (%)	**PPV** (%)	**NPV** (%)
Raghu et al. (Raghu et al. 1999)	59 (29 UIP by SLB)	78	90	88	82
Hunninghake et al. (Hunninghake et al. 2003)	91 (54 UIP by SLB)	74	81	85	67
Flaherty et al. (Flaherty et al. 2003)	96 (only NSIP & UIP)	37	100	100	30

Furthermore, a recent analysis of the HRCT scans from subjects enrolled in the GIPF-001 trial confirmed that local site interpretations have a high congruity to a central radiology core. In this multi-center study, 263 HRCT scans were read as definite IPF; a retrospective central radiology core review found 93.2% to be consistent with IPF (Lynch et al. 2005). We will also take several additional steps to insure that the local HRCT reads are accurate, including:

1. A detailed training module has been developed and must be completed by each site radiologist prior to site initiation.
2. The first 10 HRCT scans from each site will be reviewed centrally to be certain that local reads are congruent with a central interpretation. If discrepancies are identified, additional education will be provided and HRCT scans will continue to be reviewed centrally until the central radiology core is confident that the local site is performing appropriately.
3. Random scans will be reviewed concurrently from each center throughout the study to confirm that the local read continues to agree with central interpretation. If discrepancies are identified, they will be addressed as in #2 above.

HRCT scans not definitive for a diagnosis of IPF will require review of a surgical lung biopsy for confirmation. Biopsies will be reviewed by a local pathologist at the clinical center as well as by a member of the central pathology review committee. If both diagnoses are the same, then that diagnosis will be considered final. If they do not agree, then a third

pathologist, another member of the central pathology review committee, will be consulted, and the majority diagnosis will be accepted. If no consensus can be reached by two of the three pathologists, the subject will not be eligible for enrollment.

In all cases, if a subject has a lung biopsy sample, that sample will be reviewed by the local and central pathologists. Therefore, the only cases that would not be subject to a direct central review process are those where the HRCT meets the centrally defined criteria for a diagnosis of definite IPF and a lung biopsy sample is not available. If a subject has an HRCT scan not read as definite IPF and no lung biopsy sample is available, the subject will not be eligible for enrollment. The table below (Table 3) summarizes the possible combinations for making a diagnosis.

If a lung biopsy sample is available, the subject is not eligible for enrollment until a consensus statement is received from the pathology reviewers.

Table 3: Combining High-resolution Computed Tomography and Pathology Interpretations to Determine if Idiopathic Pulmonary Fibrosis is Present

HRCT Diagnosis	Pathology Diagnosis	Diagnosis of IPF?
Definite UIP	Definite UIP	Yes
Definite UIP	Probable UIP	Yes
Definite UIP	Possible UIP	Yes
Definite UIP	Not UIP	No
Definite UIP	Unavailable	Yes
Consistent with UIP	Definite UIP	Yes
Consistent with UIP	Probable UIP	Yes
Consistent with UIP	Possible UIP	No
Consistent with UIP	Not UIP	No
Consistent with UIP	Unavailable	No
Suggests alternative Dx	Any Path	No

5.3. Exclusion Criteria

1. Current enrollment in another investigational protocol
2. Screening or enrollment 6MWD of < 50 meters
3. Difference > 15% between first and second enrollment 6MWD
4. Acute or chronic impairment other than dyspnea (eg, angina pectoris, intermittent claudication) limiting the ability to comply with walk test or other study requirements
5. Forced expiratory volume1/FVC ratio < 0.65 after administration of bronchodilator
6. Extent of emphysema greater than the extent of fibrotic change (honeycombing, reticular changes) on HRCT scan
7. Acute myocardial infarction within the past 6 months
8. Nitrate use
9. Hypersensitivity to sildenafil or any component of the formulation
10. Presence of aortic stenosis (AS)
11. Life-threatening arrhythmia within 1 month of evaluation
12. Poorly controlled diabetes mellitus requiring insulin therapy
13. Second-degree or third-degree atrioventricular (AV) block on electrocardiogram
14. Severe chronic heart failure: defined by left ventricular ejection fraction (EF) < 25%
15. Presence of idiopathic hypertrophic subaortic stenosis (IHSS)
16. Hypotension (systolic blood pressure [SBP] < 100 mm Hg or diastolic blood pressure [DBP] < 50 mm Hg); (symptomatic orthostatic hypotension)
17. Uncontrolled systemic hypertension (SBP > 180 mm Hg or DBP > 100 mm Hg)
18. Known penile deformities or conditions (eg, sickle cell anemia, multiple myeloma, leukemia) that may predispose to priapism
19. Aspartate aminotransferase (AST)/serum glutamic pyruvic transaminase (SGPT) or alanine aminotransferase (ALT)/serum glutamic oxaloacetic transaminase (SGOT) > 3 times the upper limit of normal ranges
20. Renal impairment: creatinine clearance < 30 mL/minute
21. Current drug or alcohol dependence
22. Retinitis pigmentosa
23. History of vision loss
24. History of nonarteritic ischemic optic neuropathy

25. Recently initiated pulmonary rehabilitation within 30 days of enrollment. Subjects will be prohibited from starting pulmonary rehabilitation during the trial. Subjects who are currently undergoing maintenance pulmonary rehabilitation at study entry will be asked to maintain their levels of rehabilitation for the duration of the trial.
26. Any investigational therapy as part of a clinical trial for any indication, within 30 days of enrollment
27. Start or change in dose of treatment for IPF investigational agent (interferon γ-1b, pirfenidone, etanercept, N-acetylcysteine, and any other investigational agent intended to treat IPF), corticosteroids, or cytotoxic agents, within 30 days of enrollment
28. Due to drug-drug interactions, the following agents will be prohibited: bosentan. Subjects taking strong CYP3A4 inhibitors (eg, azole antifungals, clarithromycin, diclofenac, doxycycline, erythromycin, imatinib, isoniazid, nefazodone, nicardipine, propofol, protease inhibitors, quinidine, telithromycin, troleandomycin, verapamil—not an inclusive list) will be asked to stop taking the CYP3A4 inhibitor at least 30 days prior to enrollment. However, if the subject requires the CYP3A4 inhibitor (PI judgment), as long as the dose is not changed throughout the study, the subject will be allowed to concurrently take the CYP3A4 inhibitor.
29. Treatment for PH with prostaglandins (eg, epoprostenol, treprostinil), endothelin-1 antagonists (eg, bosentan, sitaxsentan, ambrisentan), or any other phosphodiesterase inhibitor (eg, tadalafil, vardenafil) within 30 days of enrollment
30. The addition or discontinuation of calcium channel blockers, digitalis, diuretics, or vasodilators within 30 days of enrollment. Dosage must be stable for 7 days prior to enrollment (except for diuretics).
31. Listed for lung transplantation
32. Supplementation with L-arginine
33. Concurrent use of grapefruit juice or St. John's wort
34. Pregnant or lactating women
35. Resting SpO_2 (oxygen saturation measured using pulse oximetry) < 92% with 6 liters of supplemental oxygen

As stated in exclusion criteria 26–30, subjects included in this study will be allowed to use prespecified concomitant medications, including investigational and conventional drugs with

the only requisite that the dose does not change, as outlined in exclusion criteria 27 and 30. Permitted agents are not expected to influence subjects' hemodynamic parameters, their 6MWT performance, or study drug blood levels. Randomization is expected to balance the groups with respect to these concurrent agents. Furthermore, inclusion of a treatment-experienced population will increase the generalizability of the study.

Study drug will be used with caution in subjects taking alpha-blockers; may cause hypotension. Safety of this combination may be affected by other anti-hypertensives and intravascular volume depletion. Subjects should be hemodynamically stable prior to initiating therapy. Precautions will be taken in subjects with penile implants (e.g. consultation with urology specialist) before initiation of study drug.

With the current lung allocation system, the mean waiting time for lung transplantation, once the person is listed, is approximately 3 months. In order to limit study dropouts, subjects listed for lung transplantation will be excluded from this study.

5.4 Study Design and Study Visits

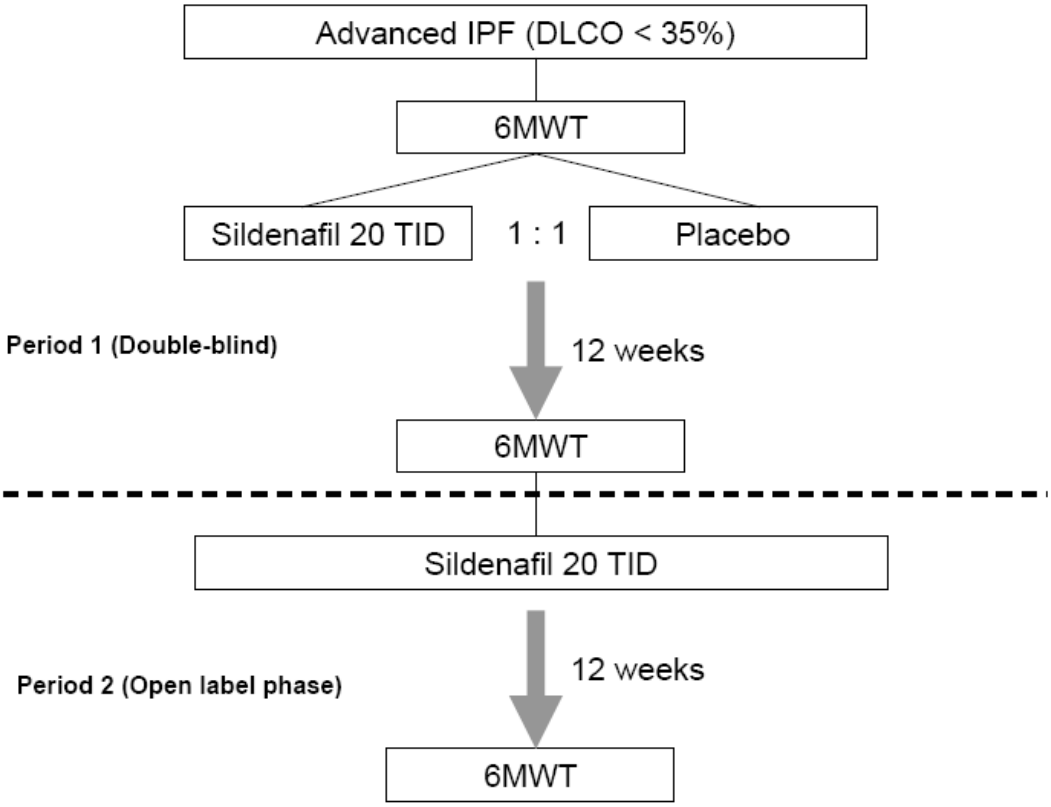

Figure 5.3: Outline of Study Design

5.4.1. Study Design Summary

Enrolled subjects will undergo a baseline 6MWT and have clinical data and blood collected. Subjects will then be given sildenafil 20 mg or placebo orally 3 times per day for 12 weeks. Study visits will occur at 1, 6, and 12 weeks, with additional data collected. A 6MWT and additional clinical data and blood will be performed/collected after 12 weeks. The primary endpoint for this study will be change in 6MWD over 12 weeks. The endpoint will be dichotomized into (1) ≥ 20% improvement in 6MWD and (2) < 20% improvement in 6MWD. Subjects unable to complete the 6MWT at 12 weeks will be considered to have a < 20% improvement in 6MWD. A major secondary endpoint will be change in QOL over 12 weeks. All subjects will take part in a second 12-week open-label phase of the protocol once they have completed the first period. This second study period will assign all subjects to

sildenafil 20 mg 3 times daily and evaluate the short-term effects of treatment and longer-term (24-week) safety profile (see Figure 5.3).

5.4.2. Study Visits

Subjects who meet entry criteria will review the informed consent, a written description of the purpose, procedures, and risks of the study, with the principal investigator (PI), coinvestigator, or study coordinator, and all questions will be answered. The informed consent form will be signed by the subject at screening. No protocol-specific procedures will be performed until the subject has signed and dated an informed consent form. This includes the screening procedures.

5.4.2.1. Screening

A history and physical examination (including pulse oxygen saturation), PFTs, arterial blood gases (ABGs), HRCT, and histopathologic review (if applicable) will be performed. Subjects will then complete a questionnaire to collect contact information, demographics, medical history, current therapies, and current symptoms. An echocardiogram will be performed to evaluate cardiac function and look for AS and IHSS. A complete blood count, serum chemistry profile, urinalysis, and an electrocardiogram (ECG) and a hCG (serum) pregnancy test (in women of childbearing potential) will be obtained.

All PFTs will be conducted by study personnel not directly involved in the treatment of the subjects. For screening purposes DLco adjusted for hemoglobin will be used. The hemoglobin value will be obtained from the ABGs. If a second spriometry and DLco are required per protocol (>14 days from screening) at enrollment visits this repeat DLco will be used to determine study eligibility.

A 6MWT will be performed as described in the STEP-IPF Manual of Operating Procedures (MOOP). If the distance of this walk is less than 50m, the subject is not eligible for enrollment into the study.

At the screening visit, subjects will be tested for resting SpO_2 levels while breathing room air. Subjects with $SpO_2 \geq 88\%$ will be walked on room air. Those below 88% will receive

resting supplemental oxygen, titrated until their resting SpO_2 levels reach 92%, and then will perform the 6MWT on that oxygen flow. Subjects will walk until they complete the 6 minutes or until their O_2 levels drop below 80% for 6 seconds. Upon dropping below 80%, the walk test will be halted and the distance walked to that point will be recorded.

During subsequent visits, subjects will have their resting SpO_2 levels measured at room air. Subjects will, if applicable, also have their resting SpO_2 levels measured on the same oxygen flow as assigned at the screening visit. Subjects whose resting SpO_2 levels do not reach 88% while receiving the assigned oxygen flow will not be walked and will have a zero recorded for their 6MWD. Subjects at or above 88% will walk (after receiving the oxygen flow assigned at the screening visit) until they complete 6 minutes or until their O_2 levels drop below 80% for 6 seconds. The distance walked will be recorded.

Subjects with symptomatic orthostatic hypotension at the screening visit will be excluded from the study. Subjects with asymptomatic orthostatic hypotension at screening may still be enrolled in the trial.

5.4.2.2. Enrollment

Eligible subjects will return for enrollment. The enrollment visit will occur no more than 6 weeks after the screening evaluation is completed. If oxygen was newly prescribed during the screening oxygen titration 6MWT, at least 7 days must separate the onset of oxygen use and the enrollment visit. Subjects will undergo a targeted history and physical examination.

Subjects will undergo two 6MWTs on the oxygen flow assigned at screening. If the distance between these two walks is greater than 15%, the subject is not eligible for enrollment. If the distance of either of the two walks is less than 50m, the subject is not eligible for enrollment. At each walk, the Borg dyspnea scale (BDS) will be measured.

PFT and ABG measurement will be performed, and blood will be drawn for a BNP level measurement. If consent has been given, blood will be drawn for research purposes. The gender sub study, QOL and dyspnea questionnaires will be completed, and NYHA functional classification obtained. Female subjects of child-bearing potential will be instructed to use 2

forms of nonhormonal contraception throughout the study duration. Also the evaluation of orthostatic hypotension will occur prior to administration of study drug and 1 hour after administration of study drug.

During the enrollment visit, subjects will receive training in the proper administration and storage of study drug and diary use and will receive a 6-week supply of study drug. Subjects will be instructed to start study drug at the enrollment visit. Subsequent study visits (1, 6, and 12 weeks) will be scheduled from the start date of study drug. One additional blood pressure measurement will be obtained 1 hour after administration of study drug on the day of enrollment.

If the enrollment visit occurs within 14 days of the screening visit, some procedures may not need to be performed at this visit, and the results of the screening measurements may be used as the enrollment measurements.

5.4.2.3. Week 1

All subjects will return at week 1 for a targeted medical history, physical examination, and laboratory values (CBC and serum chemistries) to monitor for side effects. Also the evaluation of orthostatic hypotension will occur. The study diary will be reviewed and subject compliance will be assessed by pill counts. Week 1 visit will be recorded if it occurs within +/- 2 days of the subject's scheduled visit time.

5.4.2.4. Week 6

All subjects will return at week 6. In addition to the items described under the week 1 visit (with the exception of the evaluation of orthostatic hypotension), subjects will undergo a 6MWT with Borg scale measurement, PFT (spirometry and DLco), BNP measurement, QOL and dyspnea questionnaires, and functional classification. If consent has been given, blood will be drawn for research purposes. The study diary will be reviewed, and an additional 6 weeks of sildenafil will be dispensed. Compliance to the study medication will be assessed using pill counts. Week 6 visit will be recorded if it occurs within 7 days of the subject's

scheduled visit time (eg, the week 6 visit can occur anytime between 5 and 7 weeks after starting study drug).

5.4.2.5. Week 12

All subjects will return at week 12 for the final first-period study visit. The assessments for this visit will be the same as for week 6, with the addition of ABG measurement. Also the evaluation of orthostatic hypotension will occur prior to the administration of study drug and 1 hour after administration of study drug. If consent has been given, blood will be drawn for research purposes. During this visit, all subjects will be transitioned to the open-label phase of the protocol and receive a 6-week supply of sildenafil at 20 mg 3 times daily. Compliance to the study medication will be assessed using pill counts. Week 12 visit will be recorded if it occurs within 7 days of the subject's scheduled visit time (eg, the, week 12 visit can occur anytime between 11 and 13 weeks after starting study drug). One additional blood pressure measurement will be obtained 1 hour after administration of study drug.

5.4.2.6. Week 13

All subjects will return at week 13 for a targeted medical history, physical examination, and laboratory values (CBC and serum chemistries) to monitor for side effects and for research purposes. Also the evaluation of orthostatic hypotension will occur. The study diary will be reviewed, and compliance to sildenafil will be assessed using pill counts. Week 13 visit will be recorded if it occurs within +/- 2 days of the student's scheduled visit time

5.4.2.7. Week 18

All subjects will return at week 18 for a targeted medical history, physical examination, and laboratory values (CBC and serum chemistries) to monitor for side effects. If consent has been given, blood will be drawn for research purposes. Subjects will undergo a series of assessments, including a 6MWT with Borg scale measurement, PFT, BNP measurement, QOL and dyspnea questionnaires, and functional classification. The study diary will be reviewed and an additional 6 weeks of sildenafil will be dispensed. Compliance to the study medication will be assessed using pill counts. Week 18 visit will be recorded if it occurs within 7 days of the subject's scheduled visit time (eg, the, week 18 visit can occur anytime between 17 and 19 weeks after starting study drug).

5.4.2.8. Week 24

All subjects will return at week 24 for a targeted medical history, physical examination, and laboratory values (CBC and serum chemistries) to monitor for side effects. If consent has been given, blood will be drawn for research purposes. Subjects will undergo a series of assessments, including a 6MWT with Borg scale measurement, PFT (spirometry and DLco), ABG measurement, BNP measurement, QOL and dyspnea questionnaires, and functional classification. The study diary will be reviewed, and compliance to the study medication will be assessed using pill counts. Week 24 visit will be recorded if it occurs within 7 days of the subject's scheduled visit time (eg, the week 24 visit can occur anytime between 23 and 25 weeks after starting study drug).

5.4.2.9. Week 28

All subjects will receive a follow-up phone call for updates on outstanding AEs and serious adverse events (SAEs).

5.4.2.10. Long Term Follow up

Following the above visits, subjects will have no further study visits. However, study staff will conduct a long-term follow up 5 years after the subject completes the study visits. There are no plans to contact the subject directly during this follow up. Study staff will be asked to collect survival information from the social security death index or other forms of public information.

Table 4. Table of Study Visits

	Screen	Enroll	Wk 1	Wk 6	Wk 12	Wk 13	Wk 18	Wk 24	Wk 28
Informed consent	X								
Medical history	X	X	X	X	X	X	X	X	
Physical exam	X	X	X	X	X	X	X	X	
Additional blood pressure		X			X				
Pulmonary function testing	X[1]	X[2,3]		X[3]	X[3]		X[3]	X[3]	
HRCT	X[5]								
Review surgical lung biopsy (if applicable)	X								
ABG	X	X[2]			X			X	
Pregnancy test	X								
ECG	X								
6MWT and Borg scale	X	X[6]		X	X		X	X	
Complete blood cell count and serum chemistries	X	X[2]	X	X	X	X	X	X	
Urinalysis	X								
Research blood draw and urinalysis (if consent granted)		X		X	X		X	X	
ECHO	X								
BNP		X		X	X		X	X	
Evaulation for orthostatic hypotension	X	X[7]	X		X[8]	X			
QOL assessment (SF-36, EuroQol, St. George's Respiratory Questionnaire, and ICECAP)		X		X	X		X	X	
Gender substudy questionnaire		X							
NYHA functional classification		X		X	X		X	X	
UCSD SOBQ		X		X	X		X	X	
Evaluate for acute exacerbation		X	X	X	X	X	X	X	
Review adverse events		X	X	X	X	X	X	X	X
Review concomitant meds		X	X	X	X	X	X	X	
Dispense subject diary[4]		X	X	X	X	X	X		
Review subject diary and pill count			X	X	X	X	X	X	
Dispense study treatment		X		X	X		X		

[1] Full PFTs (spirometry with pre and post bronchodilator, lung volumes, and DLco)
[2] If the enrollment visit occurs within 14 days of the screening visit, the procedure may not need to be performed at this visit, and the results of the screening measurements may be used as enrollment measurements.
[3] Spirometry and DLco
[4] Subject may be dispensed another diary if there is no more room to record information in the one he or she has.
[5] Not necessary if acceptable HRCT (please see STEP IPF MOOP for criteria) available within 3 months of screening
[6] Two walks prior to enrollment with at least 1 hour between walks
[7] Evaluate pre and post study drug administration – blinded phase
[8] Evaluate pre and post study drug administration – open label phase

5.5. Dose Justification

To our knowledge there is no evidence of a dose–response relationship associated with the primary endpoint (exercise capacity) or with tolerability when using different doses of

sildenafil. The reason for this phenomenon is not clear but may be related to the complete inhibition of phosphodiesterase type 5 with the lowest dose. For this study, we chose to use sildenafil 20 mg orally *t.i.d*.

In a study of 14 subjects with IPF and PH treated with sildenafil (see section 4.1), no substantial differences in dose-response or tolerability were evident in subjects treated with sildenafil (20, 25, 40, or 50 mg) orally *t.i.d.* In a larger double-blind, placebo-controlled study, investigators randomly assigned 278 subjects with symptomatic PH to placebo or sildenafil (20, 40, or 80 mg) orally *t.i.d.* for 12 weeks. The distance walked in 6 minutes increased from baseline in all sildenafil groups; the mean placebo-corrected treatment effects were 45 m (+13.0 percent), 46 m (+13.3 percent), and 50 m (+14.7 percent) for 20, 40, and 80 mg of sildenafil, respectively ($P < 0.001$ for all comparisons). Most AEs were mild-to-moderate in intensity for all treatment groups. No clinically significant changes were seen in any laboratory variables evaluated. Forty-two subjects reported 68 SAEs. However, only 2 SAEs, left ventricular dysfunction in 1 subject receiving 20 mg of sildenafil and postural hypotension in another subject receiving a dose of 40 mg of sildenafil, were considered by the investigators to be related to the study medication (Galie et al. 2005).

5.6. Side effects

Significant adverse reactions—based upon normal doses. (Adverse effects such as flushing, diarrhea, myalgia, and visual disturbances may be increased with doses >100 mg/24 hours.)

>10%:

Central nervous system: headache (16%–46%)

Gastrointestinal: dyspepsia (7%–17%)

1% to 10%:

Cardiovascular: flushing (10%)

Central nervous system: dizziness, insomnia, pyrexia

Dermatologic: erythema, rash

Gastrointestinal: diarrhea (3%–9%), gastritis

Genitourinary: urinary tract infection

Hematologic: anemia, leukopenia

Hepatic: LFTs increased

Neuromuscular & skeletal: myalgia, paresthesia

Ocular: abnormal vision (color changes, blurred or increased sensitivity to light 3%; up to 11% with doses >100 mg)

Respiratory: dyspnea exacerbated, epistaxis, nasal congestion, rhinitis, sinusitis

< 2% (limited to important or life-threatening): abnormal dreams, allergic reaction, anemia, angina pectoris, anorgasmia, asthma, AV block, cardiac arrest, cardiomyopathy, cataract, cerebrovascular hemorrhage, cystitis, depression, dysphagia, decreased hearing, hemorrhage, cerebral thrombosis, colitis, dyspnea, edema, epistaxis, exfoliative dermatitis, eye hemorrhage, gout, heart failure, hematuria, hyperglycemia, hypoglycemia, hypernatremia, hypertension, hypotension, hyperuricemia, intracerebral hemorrhage, increased intraocular pressure, leukopenia, migraine, myocardial ischemia, MI, myasthenia, mydriasis, neuralgia, nonarteritic ischemic optic neuropathy (NAION), palpitation, photosensitivity, postural hypotension, priapism, pulmonary hemorrhage, rectal hemorrhage, retinal vascular disease or bleeding, seizure, shock, stomatitis, subarachnoid hemorrhage, syncope, tachycardia, tendon rupture, TIA, urinary incontinence, ventricular arrhythmia, vertigo, visual field loss, vitreous detachment/traction, vomiting

5.6.1 Contraindications

Hypersensitivity to sildenafil or any component of the formulation; concurrent use of organic nitrates (nitroglycerin) in any form (potentiates the hypotensive effects)

5.6.2 Warnings / Precautions

Decreases in blood pressure may occur due to vasodilator effects; use caution in subjects with resting hypotension (BP < 90/50), hypertension (BP > 170/110), fluid depletion, severe left ventricular outflow obstruction, or autonomic dysfunction, and subjects receiving alpha-blockers or other antihypertensive medication. Not recommended for use with pulmonary veno-occlusive disease.

Use caution in subjects with cardiovascular disease, including cardiac failure, unstable angina, or a recent history (within the last 6 months) of myocardial infarction, stroke, or life-threatening arrhythmia. Use caution in subjects receiving concurrent bosentan. Use caution in subjects with bleeding disorders or with active peptic ulcer disease; safety and efficacy have not been established.

Sildenafil should be used with caution in subjects with anatomical deformation of the penis (angulation, cavernosal fibrosis, or Peyronie's disease), or in subjects who have conditions which may predispose them to priapism (sickle cell anemia, multiple myeloma, leukemia).

Rare cases of nonarteritic ischemic optic neuropathy (NAION) have been reported; risk may be increased with history of vision loss. Other risk factors for NAION include low cup-to-disc ratio ("crowded disc"), coronary artery disease, diabetes, hypertension, hyperlipidemia, smoking, and age > 50 years.

Sildenafil may cause dose-related impairment of color discrimination. Use caution in subjects with retinitis pigmentosa; a minority have generic disorders of retinal phosphodiesterases (no safety information available). Safety and efficacy in pediatric subjects have not been established.

Cases of sudden decrease in hearing and hearing loss with the use of PDE5 inhibitors such as sildenafil have been reported. Investigators should advise subjects of this possible adverse reaction. Subjects should seek medical attention immediately if these symptoms occurs. Other possible symptoms with the hearing loss are tinnitus and dizziness.

As outlined in section 3.4, sildenafil appears to be generally well-tolerated in subjects with advanced lung disease. In a study of 14 subjects with IPF treated with sildenafil (see section 4.1), 2 subjects had sildenafil stopped due to side effects attributed to the medication (diarrhea and transient hypotension). In that study, 1 subject experienced chest pain during the follow up test, 1 subject complained of mild intermittent diarrhea and headaches, another complained of mild intermittent headaches, and a fourth complained of blurry vision. The remaining 8 subjects experienced no AEs. In a large trial of sildenafil for primary PH (160

subjects), most AEs were mild-to-moderate for all treatment groups. Over 12 weeks, only 2 SAEs, postural hypotension and left ventricular dysfunction, were considered to be related to sildenafil (Galie et al. 2005).

Monitoring for side effects will include questioning on every study visit and encouragement to call the investigator about headache, diarrhea, visual changes, chest pain, palpitations, worsening dyspnea, peripheral edema, diaphoresis, and dizziness. As outlined in section 5.3, subjects with unstable cardiovascular disease or pre-existing ophthalmologic conditions will be excluded from the study. On every study visit, investigators will obtain a medical history and perform a complete physical examination. One additional blood pressure measurement will be obtained 1 hour after administration of study drug on the day of enrollment and on week 12 visit.

Orthostatic hypotension has occurred rarely in subjects receiving sildenafil (<2%), with a similar rate reported by those receiving placebo (Zusman RM et al. Am J Cardiol 1999; 83:35C). To monitor for this unlikely but potential complication, an orthostatic hypotension evaluation will be performed at screening, enrollment (pre and post study drug administration), wk 1, wk 12 (pre and post sildenafil administration), and wk 13 visits.

Beginning with the enrollment evaluation, subjects with symptomatic orthostatic hypotension will be discontinued from study drug but may remain in the trial. Symptoms of orthostatic hypotension are those that develop on assuming the erect posture and usually resolve on resuming the recumbent position. They may include lightheadedness, dizziness, blurred vision, weakness, fatigue, cognitive impairment, nausea, palpitations, tremulousness, headache, and neck ache.

5.6.3 Study Drug Discontinuation

Study drug will be stopped in any subject with SBP < 100 mm Hg or DBP < 50 mm Hg. Subjects with chest pain, palpitations, worsening peripheral edema, S3 gallop, or diaphoresis will have a 12-lead ECG and a 2D-echocardiogram performed as soon as possible. Study

drug will be stopped in subjects with acute coronary syndromes, AV block, life-threatening arrhythmias, left ventricular dysfunction (EF < 25%), or clinically significant visual changes.

5.7. Recruitment Procedures

Subjects recruited for this study will be physician-referred or self-referred to participating centers in the IPFnet. Each site within IPFnet has a well-developed infrastructure of local pulmonologists within the surrounding geographic area. These pulmonologists are kept informed of ongoing IPF clinical trials and regularly refer subjects to studies conducted at IPFnet clinical centers.

Additional steps will be taken to inform clinicians of the trials in progress within IPFnet, including: presentations at faculty staff meetings at local hospitals, medical grand rounds, and national conferences; direct mail notification; monthly faxes; and advertisement of IPFnet trials in pulmonary journals.

Clinical center subjects previously diagnosed with IPF will be notified of the trials by mail whenever possible.

Recruitment of minorities and women will be monitored by the Data Coordinating Center (DCC) and Data and Safety Monitoring Board (DSMB). If necessary, additional recruitment efforts will be made at specific centers to ensure that the aggregate subject sample contains appropriate representation of women and minorities.

5.8. Study Procedures

The following procedures are detailed in the IPFnet STEP-IPF MOOP accompanying this protocol:

1. PFT
2. ABG
3. HRCT scan of the chest (including imaging of pulmonary arteries)
4. Complete blood count and serum chemistries
5. Pregnancy test/quantitative β-HCG
6. ECG

7. 6MWT/BDS
8. Echocardiogram
9. BNP
10. QOL questionnaires (EuroQol, SF-36, St. George's Respiratory Questionnaire, and ICECAP)
11. Gender sub study questionnaire
12. University of California at San Diego Shortness of Breath Questionnaire (UCSD SOBQ)
13. NYHA functional classification
14. Evaluation for orthostatic hypotension

5.8.1. Biological Specimen Management

5.8.1.1. Biological Specimen Sample Management

Subjects who consent to having blood drawn for research purposes and for the banking of blood, blood components, and other biologic specimens (urine and bronchoalveolar lavage fluid) will have approximately 40.5 mL of blood drawn, 17 mL blood drawn for DNA and 20 mL of urine collected at enrollment visit. Subjects will have approximately 50 mL of blood drawn and 20 mL urine specimen collected at each 6-week follow up visit. During suspected AEx subjects will have approximately 35 mL of blood drawn for research purposes and other clinically obtained biologic specimens (BAL) that would otherwise be discarded will be collected whenever possible. Blood specimens will be separated according to STEP IPF MOOP guidelines into the following components for banking in the repository; serum, plasma and DNA. Coding of all biologic-specimens for the repository will be performed by study staff at the clinical center. The samples will be processed per STEP IPF MOOP guidelines, aliquoted, labeled with barcode labels, and stored at -70°C at the clinical center. At regular intervals, samples will be batched and shipped to the central repository.

The central repository will be managed by NHLBI. The NHLBI sets up a contract with a company that can perform repository functions for NHLBI trials. IPFnet has been granted permission to utilize this resource.

Samples shipped to the NHLBI repository will be labeled with barcode labels, no demographic information or subject identifiers will be included on the label. The only identifier will be a sample ID. This sample ID will be linked in the DCC clinical database to subject information. No subject information will be transferred to the biological specimen database.

The subject's samples may be utilized for approved substudies relating to human disease, including, but not limited to, IPF. The studies for which an individual's samples will be made available will be determined by the subject's answers to questions on the biological sample informed consent form. The subjects can choose to make their samples available for all options or any combination. Samples will be made available to researchers only with IPFnet Steering Group approval until such time as the samples are made public through the NHLBI repository.

5.8.1.2. Acute Exacerbation Sample Management

Subjects will be given an AEx kit to carry with them to the hospital or doctor's office when they have an episode of suspected AEx. The kit will include tubes to collect blood. If a subject presents to their local clinical center with a suspected AEx in addition to collecting blood we will collect other biologic specimens (BAL) collected from clinically performed procedures (specimens that would otherwise be discarded).

5.9 Concomitant Medications

The following medications will not be allowed during the course of the study: alpha-blockers (eg, doxazosin), bosentan, CYP3A4 inhibitors (eg, azole antifungals, clarithromycin, diclofenac, doxycycline, erythromycin, imatinib, isoniazid, nefazodone, nicardipine, propofol, protease inhibitors, quinidine, telithromycin, troleandomycin, and verapamil—not an inclusive list), prostaglandins (eg, epoprostenol and treprostinil), endothelin-1 antagonists (eg, bosentan, sitaxsentan, and ambrisentan), and any other phosphodiesterase inhibitor (eg, tadalafil and vardenafil).

5.10 Laboratory Testing

Clinical laboratory parameters will be assessed throughout the study. The following tests will be performed at the time points specified in the protocol: chemistry (albumin-globulin ratio);

ALT (SGPT); AST (SGOT); albumin; alkaline phosphatase; amylase; bilirubin—direct, indirect, and total; blood urea nitrogen (BUN); BUN/creatinine ratio; calcium; carbon dioxide; total cholesterol; chloride, total creatine phosphokinase; creatinine; gamma-glutamyltransferase; globulin; glucose; total iron; lactate dehydrogenase; lipase; magnesium; inorganic phosphorus; potassium; total protein; sodium; total iron-binding capacity; triglycerides; uric acid) and hematology (red cell count, white cell count, hemoglobin, hematocrit, cell indices, differential, platelet count).

6. STUDY ENDPOINTS

6.1. First-period Endpoints

1. Change in 6MWD from enrollment to weeks 6 and 12 (dichotomized as ≥ 20% improvement or < 20% improvement)
2. Change in 6MWD from enrollment to weeks 6 and 12
3. Change in QOL from enrollment to weeks 6 and 12
4. Change in NYHA class from enrollment to weeks 6 and 12
5. Change in dyspnea using Borg scale from enrollment to weeks 6 and 12
6. Change in dyspnea using UCSD SOBQ from enrollment to weeks 6 and 12
7. Change in O_2 desaturation measures (time, distance, recovery time) during 6MWT from enrollment to weeks 6 and 12
8. Change in FVC and DLco from enrollment to weeks 6 and 12
9. Change from enrollment in resting PaO_2, SpO_2, oxygen saturation (SaO_2), and A-a gradient from enrollment to week 12
10. Change in BNP level from enrollment to weeks 6 and 12
11. AEx of IPF
12. Number of all-cause hospitalizations
13. Survival time

6.2. Second-period Endpoints

1. Changes in 6MWD from enrollment to week 24
2. Changes in QOL from enrollment to week 24

3. Change in NYHA class from enrollment to week 24
4. Changes in dyspnea using Borg scale from enrollment to week 24
5. Changes in dyspnea using UCSD SOBQ from enrollment to week 24
6. Changes in O_2 desaturation measures (time, distance, recovery time) during 6MWT from enrollment to week 24
7. Changes in FVC, DLco from enrollment to week 24
8. Changes from enrollment in resting PaO_2, SpO_2, SaO_2, and A-a gradient from enrollment to week 24
9. Changes in BNP level from enrollment to week 24
10. AEx of IPF
11. Number of all-cause hospitalizations
12. Survival time

6.3. Acute Exacerbations

The following 3 criteria will define AEx in subjects with acute worsening of their respiratory conditions:

1. Clinical (all of the following required):
   A) Unexplained worsening of dyspnea or cough within 30 days, triggering unscheduled medical care (eg clinic, study visit, hospitalization)
   B) No clinical suspicion or overt evidence of cardiac event, pulmonary embolism, or deep venous thrombosis to explain acute worsening of dyspnea
   C) No pneumothorax

2. Radiologic/Physiologic (only 1 of the following required):
   A) New ground-glass opacity or consolidation on computed tomography (CT) scan or new alveolar opacities on chest x-ray
   B) Decline of ≥ 5% in resting room air SpO2 from last recorded level OR decline of ≥ 8 mm Hg in resting room air PaO2 from last recorded level

3. Microbiologic (all of the following required):
   A) No clinical evidence for infection (ie, absence of grossly purulent sputum, fever > 39°C orally)

B) No microbiologic evidence of infection (ie, clinically significant bacterial growth on sputum or endotracheal aspirate cultures, quantitative culture by protected brush specimen $\geq 10^3$ cfu/mL or bronchoalveolar lavage $\geq 10^4$ cfu/mL or the presence of specific pathogens on stains of any of the above)

6.4. Identification of Acute Exacerbation

All subjects will be educated regarding the importance of identifying AEx. At the time of enrollment, subjects will be educated to the possibility of developing acute symptomatic worsening that might represent an AEx of IPF and instructed to contact their study site coordinator within 48 to 72 hours of the apparent event.

All subjects will be questioned about any change in dyspnea or cough and any interim clinic visits or hospitalizations. Finally, as part of the IPFnet outreach to community referring-physicians, the importance of AExs will be emphasized. When a subject is identified who meets criteria 1A, this will trigger the collection of additional clinical data to evaluate a suspected AEx. These data will be collected as part of standard clinical care (i.e., this protocol does not require collection of all items). Items collected as part of standard of care for suspected AEx include:

- IPFnet AEx case report form (CRF) (required)
- Chest x-ray, CT scan with/without pulmonary angiogram (reports should be faxed and followed by hard copies or discs)
- Oxygen saturation (pulse oximetry)
- ABG
- Respiratory cultures (sputum, endotracheal aspirate, and lavage)
- Blood cultures
- Clinic/hospital records related to the event

All potential cases of AEx will be reviewed by the site PI first, and a decision on whether the case may represent an AEx will be made. If AEx is suspected, the case will be sent to the IPFnet Adjudication Committee, which will assign a final diagnosis (see Table 5). If there is disagreement among members, the majority opinion will be recorded.

During episodes of suspected AEx, as determined by the individual site investigator, treatment with study drug will be withheld. Subjects will remain blinded and in the study unless the attending physician responsible for the subject's acute medical care and the DCC medical monitor feel unblinding is needed for subject safety reasons.

Table 5: Final Diagnoses in Evaluation of Suspected Acute Exacerbations

Definite acute exacerbation	All criteria met; no alternative etiology
Unclassifiable acute worsening	Insufficient data to evaluate all criteria; no alternative etiology
Not acute exacerbation	Alternative etiology identified that explains acute worsening

An AEx will be treated at the discretion of the treating physician. Standard of care generally involves evaluation for respiratory infection, pulmonary embolism, cardiac events, and pneumothorax; and treatment with intravenous corticosteroids. Because the standard of care for management of suspected AExs includes steroids, the following dose will be recommended: intravenous solumedrol—1.0 g/day (4 equally divided doses) for 3 days, 0.5 g/day (2 equally divided doses) for 3 days, and 1.0 mg/kg/day for 3 days, with subsequent 0.5 mg/kg/day of oral prednisone tapered off over the remainder of 2 weeks.

Study drug will be resumed at presuspected AEx doses after subjects clinically improve, as confirmed by the local PI. Subjects unable to return to the study site after suspected AEx due to medical frailty (eg, continued institutionalization and progressive disability) will be categorized as failing to improve 20% on 6MWD in secondary analyses.

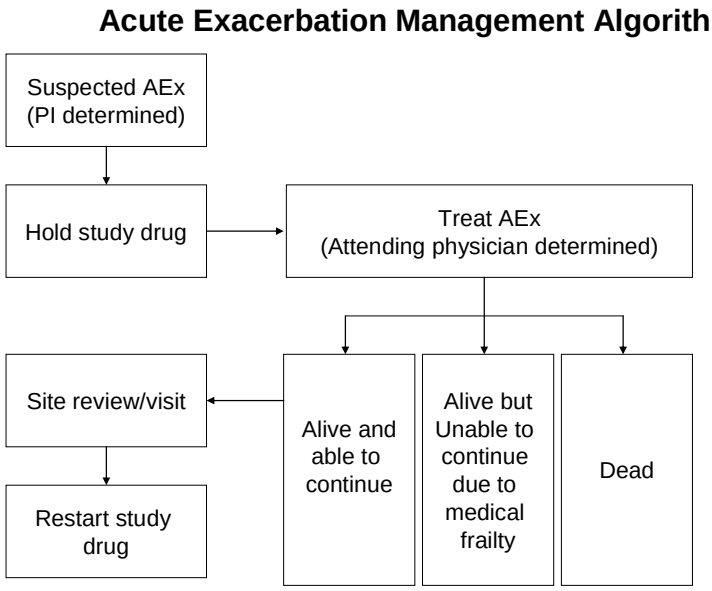

Figure 6.1: Acute Exacerbation Flow Chart

7. SAFETY ASSESSMENTS

7.1. Adverse Events

During a clinical trial, the reporting of adverse event information can lead to important changes in the way a new treatment is developed, as well as provide integral safety data.

7.2. Definitions

An adverse event (AE) is any untoward medical occurrence in clinical-investigation subject administered a pharmaceutical product. An AE does not necessarily have a causal relationship with this study drug. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered to be related to the medicinal product. Diseases, signs, symptoms, or laboratory abnormalities already existing at enrollment are not considered AEs unless they worsen (ie, increase in intensity or frequency). Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required

may be an AE. Surgical procedures planned prior to randomization and the conditions leading to these measures are not AEs.

A serious adverse event is any untoward event that:

- is fatal
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization, with the following exceptions:
    - Preplanned (prior to the study) hospital admissions unless the hospitalization is prolonged
    - Planned admissions (as part of a study, eg, routine biopsies)
    - 23-hour rehospitalizations
    - Hospitalization for elective procedure
    - Emergency room visits
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- important medical events that may not result in death, be life-threatening, or require inpatient hospitalization may be considered an SAE when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Life-threatening means that the subject was, in the view of the investigator, at immediate risk of death from the AE as it occurred. It does not include an AE that, had it occurred in a more severe form, might have caused death.

Persistent or significant disability/incapacity means that the event resulted in permanent or significant and substantial disruption of the subject's ability to carry out normal life functions.

Associated with the use of the drug means that there is a reasonable possibility that the experience may have been caused by the drug.

7.3. Adverse Event Collection

For the IPFnet STEP-IPF trial, all AEs (serious and nonserious) will be recorded from start of study treatment through final study visit on the AE CRF. All SAEs will be recorded from start of study treatment through 28 days after discontinuation of study drug.

7.4. Procedures for Reporting a Serious Adverse Event

For the IPFnet STEP-IPF trial, all deaths and all SAEs require expedited reporting. The investigator must complete and submit a Pfizer Investigator Initiated Research (IIR) form to DCRI Safety Surveillance within 24 hours of knowledge of the event.

DCRI Safety Surveillance
Telephone: 1-866-668-7799
Fax: 1-866-668-7138

The investigator must complete and submit a follow-up IIR form when important follow-up information (diagnosis, outcome, results of specific investigations, etc.) becomes available after submission of the initial form. Follow-up forms should be submitted according to the same process used for reporting the initial event as described above (ie, within 24 hours of knowledge). All reportable events will be followed until resolution, stabilization, or 30 days after the last subject enrolled has completed their last study visit, whichever occurs first. The investigators will be responsible for reporting AEs to their local institutional review boards (IRBs) in accordance with local guidelines.

DCRI Safety Surveillance will forward the IIR forms to the DSMB chair, the NHLBI representative and Pfizer U.S. Clinical Safety within 1 to 2 business days.

Regulatory Reporting

AEs that meet the criteria of serious, study drug-related, and unexpected per the U.S. package insert, qualify for expedited reporting to the regulatory authorities. The DCRI Safety Surveillance Medical Monitor will perform a medical review of all SAEs submitted and evaluate for “unexpectedness.” DCRI Safety Surveillance will confirm unexpectedness of the

event with the site. Site investigators are required to complete and submit the voluntary form 3500 MedWatch online for the events identified as serious, drug-related, and unexpected at https://www.accessdata.fda.gov/scripts/medwatch/.

7.5. Unblinding Procedures

The DCC Medical Monitor will be available to the study physician to help consider the need for unblinding on a case-by-case basis. Unblinding will be permitted ONLY for subject safety. Specifically, the blind should be broken only for serious, unexpected, and drug-related AEs or when required by local regulatory authorities, when the knowledge of treatment assignment is needed for subject safety. The site investigator must notify the DCC before unblinding any subject. The site investigator must notify the Medical Monitor at the DCC to begin the unblinding process for any subject. In an emergency, if the clinical center investigator is not immediately available, the attending physician may contact the DCC Medical Monitor directly. Emergency contact wallet cards will be provided to all study subjects.

Contact Information for DCC Medical Monitor(s):
Pager number: 919-970-7435

8. STUDY DRUG PROCEDURES

At the baseline, 6-week, 12-week, and 18-week study visits, subjects will receive a supply of study drug sufficient to last for 6 weeks.

9. DATA MANAGEMENT

9.1 Hardware and Software Configuration

9.1.1. Hardware and Database Software

Data will be stored in an Oracle database system. Oracle has advantages of processing efficiency and smooth linkage with other software systems. The application and database will be hosted on Solaris Unix servers at the DCC. Clintrial will be used for data entry.

9.1.2. Statistical Software

SAS will be used as the principal application for the management of analysis data files and statistical computations. S-Plus will be used to provide supplementary functions as needed.

9.1.3. Access Control and Confidentiality Procedures

Access to databases will be controlled centrally by the DCC through user passwords linked to appropriate privileges. This protects the data from unauthorized changes and inadvertent loss or damage.

9.1.4. Security

Database and Web servers will be secured by a firewall and through controlled physical access. Oracle has many security features to ensure that any staff member accessing the database has the proper authority to perform the functions he or she requests of the system. Within the secondary SAS databases, Unix group-access control maintains similar security. The Sun workstation login is secured by extensive user-password facilities under Unix.

9.1.5. Back-up Procedures

Database back-up will be performed automatically every day, and standard DCC policies and procedures will be applied to dictate tape rotation and retention practices.

9.1.6. Virus Protection

All disk drives that provide network services, and all user computers, will be protected using virus-scanning software. Standard DCC policies will be applied to update these protection systems periodically throughout the study.

9.2. Sources of Data

Data will be captured and forwarded to the DCC from the sites and the adjudication committees. First, basic clinical information, (eg, demographic information), will be recorded on paper CRFs and forwarded via parcel-delivery service to the DCC for data entry.

9.3. Data Management Activities

In general, the following data management procedures will be applied:

1. Paper CRFs will be designed specifically for the needs of this study. The CRF will be partitioned into "booklets" according to the type of data captured (eg, screening and clinical data). Identification information will identify key fields, eg, the participant's ID number, initials, and date of birth, as well as the date of the evaluation.
2. The CRF will be printed on 3-part NCR paper. At regular intervals, the different parts of the CRF will be separated. One part will remain at the clinical sites while the others will be forwarded to the DCC using a parcel-delivery system.
3. Personnel at clinical sites will record the data mandated by the protocol on the CRFs. They will be abstracted from the participant's medical charts and other source documents. All CRFs will be completed according to the current Good Clinical Practice (GCP) guidelines. Training on completing the CRFs will be included in the training session described in the IPFnet STEP-IPF MOOP.
4. A database will be created on the DCRI computer network specifically for this study. As described above, the database will be managed with Oracle using Clintrial.
5. For every record type, the data dictionary will identify key fields (eg, the participant's ID number and the type and date of evaluation), the field type (eg, numeric, character, checklist, or date), and ranges for impossible and improbable values.
6. All CRFs will be entered into the study database. Double data-entry by 2 different operators will be performed to ensure a high level of confidence in the data entered.

A series of computerized validation checks will be performed at the DCC. "Queries" will be generated, and data clarification forms (DCFs) for problems and exceptions uncovered will be forwarded to the clinical sites for investigation and resolution. Corrections will be made on the DCF using current GCP standards and forwarded to the DCC. If corrections are needed to the CRF form prior to the initial submission to the DCC, a single line will be drawn through the original entry such that the original entry is still visible. The correct value will be written close to the field and the correction initialed and dated by the IPFnet staff member making the change.

9.4. Data Quality Control Procedures

Four levels of database quality control will be performed. The first level is the double data-entry process as described above. The second level consists of programmatic consistency checks and/or range checks. The third level of database quality is a record or panel level of control. Programs will be written to identify suspected duplicate, blank, or missing records and records not double-entered within and across database tables. An independent auditing group will perform the fourth level of database quality control. These internal data quality and process compliance audits are routinely conducted on internal ongoing studies to document the frequency of random errors and identify systematic deviations so that they can be corrected. Other periodic quality control checks will document the frequency of random entry errors and identify systematic and process errors.

In general, the following issues will be addressed:

1. Data completeness: completion by the clinical centers of all evaluations mandated by the protocol
2. Procedural errors: errors in performing study procedures (eg, taking the blood samples)

Remedial action will be taken as appropriate; otherwise, the STEP-IPF protocol and MOOP may be revised as appropriate. Training and recertification will be made available to redress deficiencies and misunderstandings.

9.5. Data Management Reports

A variety of standard progress reports will be prepared during the course of a trial and include:

- **Data Status/Exception Reports:** lag in entering CRFs into the database, missing visits, missing pages, listing of outstanding queries, and summary of totals of outstanding queries
- **Quality Control Reports:** duplicates, missing from table, blanks
- **Data Surveillance Reports:** query frequencies, perfect data
- **Protocol Deviation Reports:** numbers of ineligible participants enrolled in the study

Reports will be prepared for the periodic meetings of the Steering Group. Some reports, such as the Data Exception report, may be generated more frequently as required.

10. STUDY DESIGN AND DATA ANALYSIS

10.1. Overview of the Study Design

This double-blind, placebo-controlled, randomized trial will evaluate the benefits and risks of sildenafil in an IPF population with advanced disease defined by DLco < 35% predicted. For each subject, the primary outcome will be defined by an improvement of 20+% in 6MWD from baseline to 12 weeks.

The study is powered on the primary endpoint of 20+% improvement in 6MWD. The highest value of the 6MWD between screening and enrollment will be used as the baseline 6MWD. However, the Steering Group has identified 2 key secondary endpoints—6MWD assessed as a continuous measure and the visual analog scale of the EuroQol—that they feel are clinically important response variables for Specific Aims 1 and 2. Evidence of improvement favoring sildenafil therapy would be viewed as a clinically significant even in the absence of statistical significance for the primary endpoint.

10.2. Power Analysis

The IPFnet Steering Group has defined a clinically meaningful change in 6MWD to be a 20+% improvement over the baseline assessment. A 20+% improvement in 6MWD is expected to be a fairly rare event in an untreated population with advanced IPF. Over the initial 12 weeks of treatment, it is expected that fewer than 10% of placebo-treated subjects will have a clinically meaningful improvement in 6MWD. Based on currently available safety and efficacy data for sildenafil, a response rate of 30% or more in the sildenafil-treated group would be viewed as a clinically meaningful treatment effect.

Based on these assumptions (placebo response rate = 10%, sildenafil response rate = 30%), with an overall type I error rate of 0.05 allowing for an interim analysis and a 1:1

randomization ratio, a sample size of 170 would be sufficient to achieve 90% power. These calculations were based on a chi-square test of equal proportions.

10.3. Specification of the Primary Analyses

The primary test statistic will be based on a chi-square test comparing the rates of clinically meaningful improvement in 6MWD from baseline to 12 weeks between subjects assigned to sildenafil or placebo therapy.

10.4. Specification of Clinically Significant Secondary Analyses

Test statistics for 6MWD as a continuous measure and the EuroQOL visual analog scale will be based on a worst-rank score approach comparing overall improvement from baseline to 12 weeks between subjects randomized to sildenafil or placebo therapy (Lachin 1999).

10.5. Specification of the Analyses for the Period 1 and Period 2 Data

Walk tests will be conducted at screening; enrollment; and at 6, 12, 18, and 24 weeks. Linear models will be developed to compare the 2 treatment groups across the 24-week study period (McDermott et al. 2002). The first group of subjects will receive placebo for 12 weeks, followed by 12 weeks of open-label sildenafil. The second group of subjects will receive sildenafil during the 12-week double-blind period, followed by 12 weeks of open-label sildenafil. Shown in Table 6 are the expected values of the 6MWD parameters for the 2 periods. The parameters are defined as follows:

- π_I and π_{II} are the expected 6MWD parameters for subjects receiving placebo or no treatment in Periods I and II
- π_Δ is defined as the difference between π_{II} and π_I
- α_D and α_S are the disease-modifying and symptomatic effects expected in Period I
- α_T is the incremental effect of treatment achieved during Period II

As shown in Table 6, the treatment effect observed at the end of Period I is a combination of the symptomatic and disease-modifying effects of sildenafil therapy ($\alpha_D + \alpha_S$). By assumption, the treatment effect observed at the end of Period II is the disease-modifying effect of having been on sildenafil therapy in Period I (defined by the parameter α_D). A goal of these analyses will be to identify the symptomatic, disease-modifying, and overall effect of sildenafil therapy in an IPF population with advanced disease.

Table 6: Expectations for 6MWD Parameters in the 2-period Design

Treatment by Period	E (Period I response)	E (Period II response)	E (change between Periods I and II)
Placebo / Sildenafil	π_I	$\pi_{II} + \alpha_T$	$\pi_\Delta + \alpha_T$
Sildenafil / Sildenafil	$\pi_I + \alpha_D + \alpha_S$	$\pi_{II} + \alpha_D + \alpha_T$	$\pi_\Delta + \alpha_T - \alpha_S$

10.6. General Analytic Considerations

All analyses will be based on intent-to-treat principles using all randomized participants. Baseline factors across groups will be compared using mean (standard deviation) and median (25th and 75th percentiles) summary measures. Kaplan-Meier curves will be used to display event rates. Due to clinical interest in departures from both sides of the null hypothesis, all test statistics will be 2-sided.

10.7. Randomization, Blinding, and Reporting of Results

A permuted block randomization scheme will be created with varying block sizes stratified by clinical center. Once a subject has completed the screening and baseline period and evaluation for inclusion/exclusion criteria, the randomization process will begin. Subjects will be randomized to receive one of the 2 treatment regimes with equal probability (1:1), via telephone contact with a central interactive voice response system (IVRS), using a toll-free randomization number. On the day of randomization, after the subject has successfully met all inclusion and exclusion criteria, the investigator or designee will call the central randomization number to obtain the assigned kit randomization numbers for that subject. For resupply of the site, the IVRS will monitor minimal volume of a kit type and/or expiration date and will automatically notify the pharmacy.

The trial results will be reported according to guidelines specified in the CONSORT statement. A flow diagram describing screening, recruitment, randomization, dropout, and vital status will be included in the primary manuscript. AEs and efficacy data will be presented by the 2 treatment groups. Adherence, dropout, and lost to follow-up will be carefully examined across the 2 treatment groups. Analyses of safety will be based on data from all randomized subjects who received at least 1 dose of study drug.

10.8. Specification of Secondary Analyses

Regression models will be constructed to compare PFTs, QOL, and 6MWT parameters between the sildenafil and placebo treatment groups. To adjust for differences in the disease severity and baseline covariates, the following measures may be included in the regression models: age, sex, race, height, disease severity, and BNP level. The validity of the regression models in terms of meeting modeling assumptions will be assessed via standard modeling diagnostics and goodness-of-fit measures.

10.9. Recommendations on Interim Analyses

First and foremost, the role of the DSMB will be to review subject safety and trial conduct at periodic points during the study. The DSMB may require analyses of the primary endpoint results for weighting the benefits and risks of the treatment strategies. Because the DSMB could stop the trial for safety concerns as well as for a large efficacy benefit, there could be multiple opportunities to reject the null hypothesis (no difference in event rates between the placebo and active groups). Without adjusting the α levels for the repeated-testing environment, the probability of making a type I error can be greatly inflated over the nominal 0.05 level for the sildenafil vs. placebo comparison. The O'Brien-Fleming Spending Function will be recommended to allow for stopping if large treatment effects are observed while allowing the final significance level to be conserved at the nominal level (Lan and DeMets 1983). In Table 7, the group sequential boundaries are shown for a primary comparison with overall type I error rate set at 0.05 under the assumption that 1 interim analysis will be conducted at approximately 0.50 information time.

Table 7: O'Brien-Fleming Group Sequential Boundaries

One Interim Analysis and a Final Analysis		
Information Time	**Bound for |Z| Statistic**	**Cumulative Alpha**
0.50	2.9626	0.00305
1.00	1.9686	0.05000

Before locking the database, a statistical analysis plan (SAP) will be developed to provide complete details on the statistical analysis. Before data analysis, the SAP will be approved by

the IPFnet Steering Group and the DSMB. The SAP will include the specifics for how and when the DSMB will be notified for AEs. The DCC will deliver to the DSMB all safety data including SAEs and AEs at 6-month intervals. The DCC will prepare clinical narratives in real time and fax the clinical narrative and SAE form to the DSMB chair for review.

11. STUDY ADMINISTRATION

11.1. Cooperative Agreement Mechanism

The administrative and funding mechanism used to undertake this project is a "Cooperative Agreement" (U01), which is an assistance mechanism. Under the cooperative agreement, the NHLBI assists, supports, and/or stimulates the study and is substantially involved with investigators in conducting the study by facilitating performance of the effort in a "partner" role. The NHLBI Project Scientist serves on the Steering Group, and he or another NHLBI scientist may serve on other project committees, when appropriate. At the same time, however, NHLBI does not assume a dominant role, direction, or prime responsibility for this research program.

As described below, governance of the project is conducted through a steering group. PIs have lead responsibilities in all aspects of their trials and the project, including any modification of trial designs, conduct of the trials, quality control, data analysis and interpretation, preparation of publications, and collaboration with other investigators, unless otherwise provided for by the Steering Group.

PIs retain custody of and have primary rights to their center-specific and collaborative data, subject to government rights-of-access consistent with current Health & Human Services (HHS), Public Health Service (PHS), and NIH policies. The protocols and governance policies call for the continual submission of data centrally to the DCC for the collaborative database. At a minimum, the database will contain the key variables selected by the Steering Group for standardization across all clinical centers; procedures for data analysis, reporting, and publication; and procedures to protect and ensure the privacy of medical and genetic data and records of individuals. The NHLBI Project Scientist, on behalf of the NHLBI, will have

the same access, privileges, and responsibilities regarding the collaborative data as the other members of the Steering Group.

PIs are also encouraged to publish and to publicly release and disseminate results, data, and other products of the project, concordant with the project protocols and governance and the approved plan for making data and materials available to the scientific community and to the NHLBI. However, during or within 3 years beyond the end date of the project period of NHLBI support, unpublished data, unpublished results, data sets not previously released, or other study materials or products are to be made available to any third party only with the approval of the Steering Group.

Upon completion of the project, PIs are expected to put their intervention materials and procedure manuals into the public domain and/or make them available to other investigators, according to the approved plan for making data and materials available to the scientific community and the NHLBI for the conduct of research, at no charge other than the costs of reproduction and distribution.

The NHLBI reserves the right to terminate or curtail the project (or an individual award) in the event of (a) failure to develop or implement mutually agreeable collaborative measurement, participant eligibility, and data management sections of the protocols; (b) substantial shortfall in subject recruitment, follow-up, data reporting, quality control, or other major breech of protocol; (c) substantive changes in the agreed-upon protocols with which NHLBI cannot concur, (d) reaching a major project outcome substantially before schedule with persuasive statistical significance, or (e) human subject ethical issues that may dictate a premature termination.

Any disagreement that may arise in scientific/programmatic matters (within the scope of the award) between award recipients and the NHLBI may be brought to arbitration. An arbitration panel will be composed of 3 members—1 selected by the Steering Group (with the NHLBI member not voting) or by the individual PI in the event of an individual disagreement; a second member selected by NHLBI; and the third member selected by the other 2 members. This special arbitration procedure in no way affects the PI's right to appeal

an adverse action that is otherwise appealable in accordance with the PHS regulations at 42 CFR part 50, Subpart D, and HHS regulation at 45 CFR part 16 or the rights of NHLBI under applicable statutes, regulations, and terms of the award.

11.2. Steering Group

The Steering Group is the main governing body of the project. It is composed of clinical centers PIs, the DCC PI, the NHLBI Project Scientist and the Steering Group Chairperson. The clinical centers, the DCC, and the NHLBI each have 1 vote on the Steering Group. All decisions are determined by majority vote.

All major scientific decisions are determined by the Steering Group. It assumes overall responsibility for the design and conduct of the trial. It appoints (and disbands) committees and subcommittees as the need arises; designs, approves, and implements the study protocols; oversees the development of the STEP-IPF MOOP; monitors subject recruitment and treatment delivery; evaluates data collection and management; oversees quality assurance procedures; and implements changes and enhancements to the study as required. It also has the primary responsibility for facilitating the conduct of the trials and reporting the project's results.

11.3. Data and Safety Monitoring Board

The NHLBI will establish a DSMB in accordance with established policies (see http://www.nhlbi.nih.gov/funding/policies/dsmb_inst.htm) to ensure data quality and participant safety and to provide independent advice to the NHLBI regarding progress and the appropriateness of study continuation.

12. INVESTIGATOR AND SPONSOR OBLIGATIONS

12.1. Monitoring

Monitoring activities will be performed at all clinical centers in accordance with the DCRI standard operating procedures. Information regarding the types of visits will be outlined in the STEP-IPF MOOP.

12.2. Confidentiality and Health Insurance Portability and Accountability Act (HIPAA) Considerations

Subject confidentiality will be protected throughout the study. All subject data will be kept strictly confidential, and no subject-identifying information will be released to anyone outside the project. Confidentiality will be assured through several mechanisms. First, each subject will be assigned an anonymous study ID number, which will then be used on all study forms. Second, any study forms, blood samples, and paper records that contain subject information (eg, address lists and phone lists) will be kept at the clinical sites in secured, locked areas, coded by number. Once blood is collected, there will be no subject identifiers placed on blood samples—only the study ID number and the date of sample collection will be identified. Third, access to all subject data and information, including laboratory specimens, will be restricted to authorized personnel. In the case of computerized data, this restricted access will be assured through user logon IDs and password protection.

At the DCC only authorized personnel will have access to the study data files containing study data. Security will be assured through user logon IDs, passwords, and appropriate access privileges. Personal identifying information, such as name, address, and Social Security number, will not be entered into the DCC database. Subject-specific data reported to the Steering Group will be identified by the IPFnet ID number only.

Finally, subjects will not be identified by name in any reports or publications, nor will the data be presented in such a way that the identity of individual subjects can be inferred. Analysis files created for further study by the scientific community will have no subject identifiers. These data files will be created in accordance with the Ancillary Studies and Publication Policy of the IPFnet.

12.3. Informed Consent Procedures

All IPFnet subjects will provide written informed consent using procedures reviewed and approved by each clinical center's IRB. Informed consent will be undertaken by study personnel in person with the subject. At that point, the subject has the option of declining further participation in the study. No further study procedures will be conducted until the signed documents have been provided to the IPFnet clinical center.

Sample informed consent documents are provided to the clinical centers but will be modified according to the specific needs of the IRB at each participating clinical center.

12.4. Institutional Review Boards

Before initiating this study, the protocol, site-specific informed consent forms, HIPAA forms, recruitment materials, and other relevant information will be reviewed by a properly constituted IRB at each participating clinical center. A copy of the signed and dated IRB approval at each clinical center will be retrieved during the site initiation visit and archived at the DCC. Any amendments to the protocol, other than simple administrative and typographical changes, must be approved by each IRB before they are implemented. The sites will seek annual renewals of their IRB approvals in accordance with local procedures.

13. INVESTIGATOR AGREEMENT

I have read the foregoing STEP-IPF protocol, and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein.

I will provide copies of the protocol and all pertinent information to all individuals accountable to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the drug and the conduct of the study. I will fulfill all responsibilities for submitting pertinent information to the local IRB, if applicable, that is responsible for this study.

I further agree that NHLBI and/or DCRI will have access to any source documents from which case report form information may have been generated.

_____ _____

Signature of Principal Investigator Date

_____

Name of Principal Investigator (printed or typed)

Protocol Version 6.0 March 30, 2007
Protocol Amendment 1 Version 6.1 October 31, 2007
Protocol Amendment 2 Version 6.2 April 15, 2008

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STEP-IPF Trial
Statistical Analysis Plan

Prepared by

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Table of Contents

I. Study Summary

STEP IPF: SILDENAFIL TRIAL OF EXERCISE PERFORMANCE IN IDIOPATHIC PULMONARY FIBROSIS

This protocol proposes to test the following hypothesis: Treatment with sildenafil will improve exercise capacity and quality of life in patients with advanced idiopathic pulmonary fibrosis (IPF). This study will be completed using a 2-period study with treatment and evaluation lasting a total of 24 weeks. To address the primary hypothesis of this protocol, we propose a 12-week randomized, double-blinded, placebo-controlled trial of sildenafil in 170 patients with advanced IPF (defined by diffusing capacity of the lung for carbon monoxide [DLCO] < 35% predicted). The primary endpoint of this trial is change in 6-minute walk distance (6MWD) over 12 weeks. The second study period will be used to estimate the 24-week safety and efficacy profile of sildenafil therapy. Secondary endpoints will include change in dyspnea and quality of life. This clinical trial will be performed as part of the National Institutes of Health (NIH)/National Heart, Lung and Blood Institute (NHLBI)-sponsored Idiopathic Pulmonary Fibrosis Clinical Research Network (IPFnet).

Further explanation can be found in the STEP-IPF protocol and DSMB charter.

II. Introduction

A. Study Objectives

1. Primary

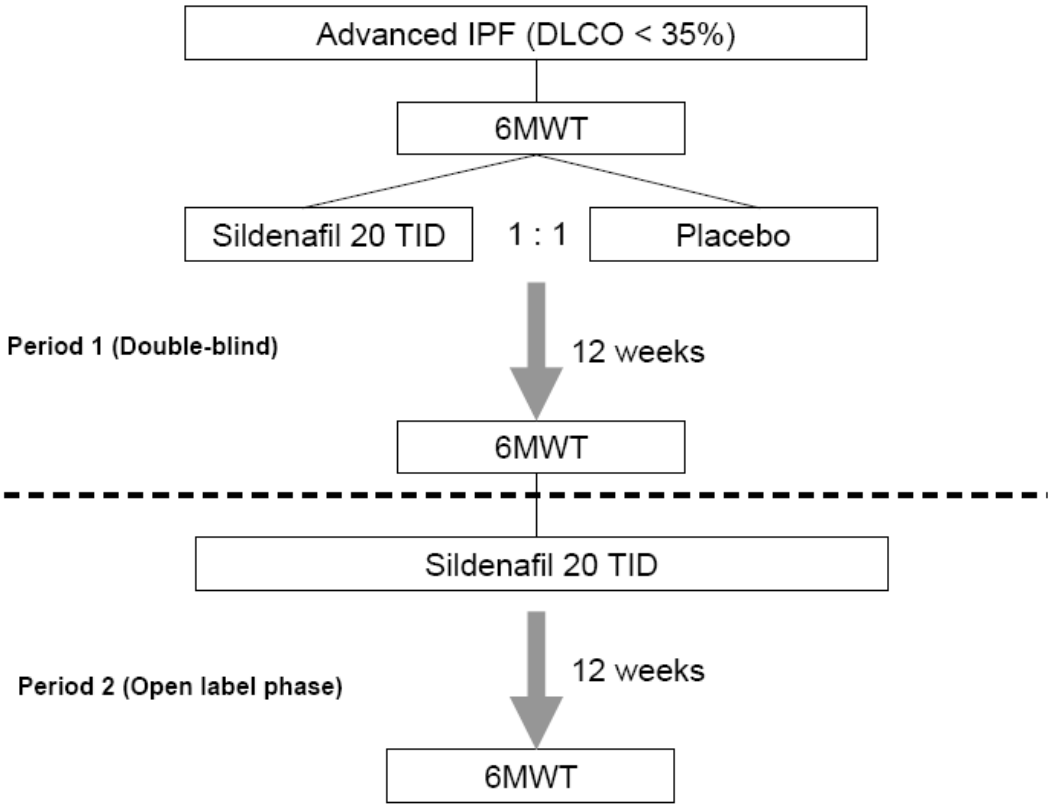
To demonstrate improved 6-minute walk test (6MWT) distance in subjects with advanced IPF treated for 12 weeks with sildenafil compared with placebo.

2. Secondary

To demonstrate improved dyspnea and quality of life in subjects with advanced IPF treated for 12 weeks with sildenafil compared with placebo.

B. Study Design

Enrolled subjects will undergo a baseline 6MWT and have clinical data and blood collected. Subjects will then be given sildenafil 20 mg or placebo orally 3 times per day for 12 weeks. Study visits will occur at 1, 6, and 12 weeks, with additional data collected. A 6MWT and additional clinical data and blood will be performed/collected after 12 weeks. The primary endpoint for this study will be change in 6MWD over 12 weeks. The endpoint will be dichotomized into (1) ≥ 20% improvement in 6MWD and (2) < 20% improvement in 6MWD. Subjects unable to complete the 6MWT at 12 weeks will be considered to have a < 20% improvement in 6MWD. A major secondary endpoint will be change in QOL over 12 weeks. All subjects will take part in a second 12-week open-label phase of the protocol once they have completed the first period. This second study period will assign all subjects to sildenafil 20 mg 3 times daily and evaluate the short-term effects of treatment and longer-term (24-week) safety profile.



C. Primary Endpoints in Support of Study Objectives

To demonstrate improved 6-minute walk test (6MWT) distance in subjects with advanced IPF treated for 12 weeks with sildenafil compared with placebo.
To demonstrate improved dyspnea and quality of life in subjects with advanced IPF treated for 12 weeks with sildenafil compared with placebo.

D. Analysis Populations

All analyses will be based on intent-to-treat principles using all randomized participants.

E. Time Table of Events and Measurement Windows

Table of Study Visits

	Screen	Enroll	Wk 1	Wk 6	Wk 12	Wk 13	Wk 18	Wk 24	Wk 28
Informed consent	X								
Medical history	X	X	X	X	X	X	X	X	
Physical exam	X	X	X	X	X	X	X	X	
Additional blood pressure		X			X				
Pulmonary function testing	X[1]	X[2,3]		X[3]	X[3]		X[3]	X[3]	
HRCT	X[5]								
Review surgical lung biopsy (if applicable)	X								
ABG	X	X[2]			X			X	
Pregnancy test	X								
ECG	X								
6MWT and Borg scale	X	X[6]		X	X		X	X	
Complete blood cell count and serum chemistries	X	X[2]	X	X	X	X	X	X	
Urinalysis	X								
Research blood draw and urinalysis (if consent granted)		X		X	X		X	X	
ECHO	X								
BNP		X		X	X		X	X	
Evaulation for orthostatic hypotension	X	X[7]	X		X[8]	X			
QOL assessment (SF-36, EuroQol, St. George's Respiratory Questionnaire, and ICECAP)		X		X	X		X	X	
Gender substudy questionnaire		X							
NYHA functional classification		X		X	X		X	X	
UCSD SOBQ		X		X	X		X	X	
Evaluate for acute exacerbation		X	X	X	X	X	X	X	
Review adverse events		X	X	X	X	X	X	X	X
Review concomitant meds		X	X	X	X	X	X	X	
Dispense subject diary[4]		X	X	X	X	X	X		
Review subject diary and pill count			X	X	X	X	X	X	
Dispense study treatment		X		X	X		X		

[1] Full PFTs (spirometry with pre and post bronchodilator, lung volumes, and DLco)
[2] If the enrollment visit occurs within 14 days of the screening visit, the procedure may not need to be performed at this visit, and the results of the screening measurements may be used as enrollment measurements.
[3] Spirometry and DLco
[4] Subject may be dispensed another diary if there is no more room to record information in the one he or she has.
[5] Not necessary if acceptable HRCT (please see STEP IPF MOOP for criteria) available within 3 months of screening
[6] Two walks prior to enrollment with at least 1 hour between walks
[7] Evaluate pre and post study drug administration – blinded phase
[8] Evaluate pre and post study drug administration – open label phase

III. Interim Analysis

One interim analysis is planned to be conducted at approximately 0.50 information time. To conserve the overall type I error rate of 0.05 the O'Brien-Fleming Spending Function will be used to

allow for stopping if large treatment effects are observed while allowing the final significance level to be conserved at the nominal level (Lan and DeMets 1983).

O'Brien-Fleming Group Sequential Boundaries

One Interim Analysis and a Final Analysis		
Information Time	**Bound for |Z| Statistic**	**Cumulative Alpha**
0.50	2.9626	0.00305
1.00	1.9686	0.05000

IV. General Analysis Conventions

A. Definition of Statistical Significance

The statistical plan will test non-directional hypotheses, i.e., all tests will be 2-sided. The level of significance for all efficacy and safety analyses will be 0.05.

B. Statistical Tests

For situations were one observation per patient is observed, like safety comparisons at individual time points, a general analysis convention will be used unless otherwise specified. For continuous and pseudo-continuous variables, treatment group differences will be tested using the Wilcoxon rank-sum test. For discrete variables, treatment group differences will be tested using the chi-square test. In the situation of low cell counts the treatment group differences will be tested using Fisher's exact method.

C. Descriptive Statistics

For continuous and pseudo-continuous variables the number of observations, number of missing values, mean, standard deviation, median, twenty-fifth percentile, and seventy-fifth percentile will be given. For yes/no, categorical, and/or ordinal variables a simple count and percent or tally will be given. Other statistics maybe considered if necessary.

D. Descriptive Plots

Descriptive plots may replace or produced in addition to descriptive statistics if deemed appropriate. If deemed necessary plots of descriptive statistics such as spaghetti, mosaic, box, cumulative distribution, loess, and etc… will be provided.

E. Study Listings

Study data will be listed by treatment group, visit if applicable, and patient where appropriate.

F. Software and Validation Procedures

All data presented in this report will be generated and validated under the guidance of the DCRI Statistical SOPs.

V. Accountability and Conduct

A. Patient Follow-up

Adherence, dropout, and lost to follow-up will be carefully examined across the 2 treatment groups. Reasons for removal from study drug or study termination will be summarized. Listing of dropout patient will be created.

B. Compliance

To monitor and evaluate patient study drug compliance, the days per week average (via pill counts) will be calculated and summarized.

C. Medications

To monitor and evaluate patient the use of prior and concomitant medications (Coded via WHO Drug) the number of observed by patient and in total will be calculated and summarized for the given WHO Drug categories. Separate summaries will be generated for prior (30 days prior to randomization) and concomitant (post -randomization) use of medications.

VI. Analyses of Demographic and Baseline Data

Patient demography such as age, weight, sex, ethnicity, and race will be summarized. The patient medical history and conditions such as duration of IPF, smoking status, coronary artery, disease, acute MI, valvular heart disease, HF, atrial fibrillation, diabetes, lung cancer, clubbing, etc… will be summarized. Measurements related to primary and secondary endpoints at baseline such as 6 minute walk test, spriometry, lung diffusion testing, ABBs, lung volume, BNP, NYHA HF class, and quality of life measures will be summarized. Treatment group differences in select demographic and clinical characteristics at baseline will be examined.

VII. Efficacy Analyses

A. Primary Efficacy Endpoint

For each subject, the primary outcome will be defined by an improvement of 20+% in 6 minute walk distance (6MWD) from baseline to 12 weeks. Since multiple 6MWDs are measured between screening and randomization, the maximum of the last two 6MWDs prior to randomization will be used as the reference to compare versus the 12 week value. The primary test statistic will be based on a chi-square test comparing the rates of clinically meaningful improvement in 6MWD from baseline to 12 weeks between subjects assigned to sildenafil or placebo therapy. In the situation of low cell counts the treatment group differences will be tested using Fisher's exact method. In addition to the comparison of baseline to 12 weeks other time intervals will be descriptively summarized such as baseline to 6 weeks, to 18 weeks, and to 24 weeks.

B. Secondary Efficacy Endpoints

1. General Descriptive Approach

For secondary efficacy endpoints a general analysis approach will be used. Three different descriptive summaries will be generated for the analysis variables. The first will consist of descriptive

statistics generated by visit on the observed values. The second will consist of descriptive statistics generated by visit on the change from baseline values. And the third will consist of spaghetti plots. Spaghetti plots are scatter plots were each patient has their own points connected. Each treatment will use a different line, symbol, and/or color.

2. General Inferential Approach

For selected time periods mixed effect regression models will be constructed to compare endpoint parameters between the sildenafil and placebo treatment groups. To adjust for differences in the disease severity and baseline covariates, the following measures may be included in the regression models: age, sex, race, height, and disease severity. The varaiance-covariance structure is assumed to be compound symmetry. The validity of the regression models in terms of meeting modeling assumptions will be assessed via standard modeling diagnostics and goodness-of-fit measures. If gross depatures are observed then transformations and/or alternate modeling procedures may be explored.

3. 6MWD and EuroQol

For 6MWD and the EuroQOL visual analog scale descriptive summaries will be generated as detailed in the general descriptive approach section. Also for 6MWD improvements from baseline (5+.10+, 20+, and 30+) will be categorized and summarized. Test statistics for 6MWD as a continuous measure and the EuroQOL visual analog scale will be based on a worst-rank score approach. For 6MWD and the EuroQOL visual analog scale inferential summaries will be generated per the general inferential approach section.

4. NYHA Heart Function Class

For NYHA HF classification descriptive summaries will be generated as detailed in the general descriptive approach section. Treatment group differences will be examined as change from baseline categories separately for each time period (0-6, 0-12, 0-18, 0-24) with the general chi-sq testing methodology.

5. Other Secondary Parameters

For the parameters shown in the following table descriptive summaries will be generated as detailed in the general descriptive approach section. For the parameters shown in the following table inferential summaries will be generated per the general inferential approach section and listing time intervals.

Other Secondary Parametes

Parameter	Time Interval			
Borg Scale Pre-Walk Rating	0-6	0-12	0-18	0-24
Borg Scale Post-Walk Rating	0-6	0-12	0-18	0-24
Resting SpO_2	0-6	0-12	0-18	0-24
FVC	0-6	0-12	0-18	0-24
FEV_1	0-6	0-12	0-18	0-24
D_LCO	0-6	0-12	0-18	0-24
BNP	0-6	0-12	0-18	0-24

NYHA Heart Function Class	0-6	0-12	0-18	0-24
UCSD Shortness of Breath Questionnaire Total Score	0-6	0-12	0-18	0-24

VIII. Safety Analyses

A. Safety Analysis Population

Analyses of safety will be based on data from all randomized subjects who received at least 1 dose of study drug.

B. Mortality

The date and cause of death will be recorded as well as days last known alive. The Kaplan Meier survival curves and death rates will be estimated at the 12 and 24 week intervals. Comparison of the treatments groups will be done with a log-rank test.

C. Acute Exacerbation

Acute exacerbation (AEx) will be identified by the site PI and then adjudicated by the IPF committee. If AEx is suspected, the case will be sent to the IPFnet Adjudication Committee, which will assign a final diagnosis. If there is disagreement among members, the majority opinion will be recorded. The final diagnosis is defined as the following:

1. **Definite acute exacerbation** - All criteria met; no alternative etiology
2. **Unclassifiable acute worsening** - Insufficient data to evaluate all criteria; no alternative etiology
3. **Not acute exacerbation** - Alternative etiology identified that explains acute worsening

The number of patients with one or move AExs will be tabulated along with the total number of distinct AEx. Comparison of the treatments groups will be done with standard categorical methods.

D. FVC Drop

For each patient post baseline FVC measurements will be compared to the baseline FVC measurement. If a post baseline FVC drop is greater than 10% then this measurement is flagged. The number of occurrences post baseline FVC drop is greater

E. Clinical Laboratory Data

Clinical lab data will be collected via a central lab and local labs, specifically ALT, AST total bilirubin, creatninine, hemoglobin, and WBC. These data will be converted to common units for each given lab. Departures from the normal range will be flagged as either below or above the normal range. These departures from the normal range will summarized for each lab measure at baseline, Period I, and Period II. Counts and percentages for patients and total events are given in the summary. Comparison of the treatments groups at a patient level will be done with standard categorical methods.

F. Adverse Experience Data

Serious and non-serious adverse events (AE) will be collected throughout patient follow-up and coded to the medra coding dictionary. The SAEs will come from the DCRI safety group's clintrace database while the non-serious AEs will come from the CRF database. Three distinct types of summaries will be produced: 1) AEs (serious + non-serious), 2) SAEs, and 3) SAEs drug related and unexpected. Each summary will have three variations: 1) All events occurring in period I and II, 2) only events occurring in period I, and 3) only events occurring in period II. The individual summaries will contain an overall line (any body system and event) followed by breakdown of each body system and preferred term name. Each line will contain two analyses, one based on a patient level and other based on an event level. The patient level will consist if the following: the number of patients with an event observed and the number of with event observed divided by the total number of randomized patients times 100. The event level will consist if the following: the number of events observed and the number of events divided by patient follow-up per 12 weeks times 100. Comparison of the treatments groups at a patient level will be done with standard categorical methods. Comparison of the treatments groups at an event level will be done with a simple binomial test.

G. Arterial Blood Gas

Three arterial blood gas variables will be include in the analysis which are PaO_2, SaO_2, and A-a gradient. A-a gradient will be defined by the following formula 0.21*(Barometric Pressure-47)-$PaCO_2$/0.8 - PaO_2 and be calculated from available data. The descriptive summaries will be generated and presented as described in the secondary endpoint analysis section. Also the inferential analysis will be generated and presented as described in the secondary endpoint analysis section for the time intervals 0-12 and 0-24.

IX. References

Lan KKG, DeMets, DL. Discrete sequential boundaries for clinical trials. Biometrika. 1983;70:659-663.

X. Table Shells

Baseline
Demographic and Risk Factor Summary

Parameter Statistic	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N=N_{EVAL}
Age (Years)			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (Q1, Q3)	xx.x (xx., xx.x)	xx.x (xx., xx.x)	xx.x (xx., xx.x)
Female	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Childbearing Potential	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Weight (kg)			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (Q1, Q3)	xx.x (xx., xx.x)	xx.x (xx., xx.x)	xx.x (xx., xx.x)
Ethnicity (Hispanic or Latino)	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Race			
American Indian or Alaska Native	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Asian	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Black or African American	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Native Hawaiian or other Pacific Islander	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
White	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Other	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Minorities [1]	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Systolic Blood Pressure (mmHg)			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (Q1, Q3)	xx.x (xx., xx.x)	xx.x (xx., xx.x)	xx.x (xx., xx.x)
Diastolic Blood Pressure (mmHg)			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (Q1, Q3)	xx.x (xx., xx.x)	xx.x (xx., xx.x)	xx.x (xx., xx.x)
Pulse (bpm)			
N (Missing)	xx (xx)	xx (xx)	xx (xx)

Baseline
Demographic and Risk Factor Summary

Parameter Statistic	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N=N_{EVAL}
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (Q1, Q3)	xx.x (xx., xx.x)	xx.x (xx., xx.x)	xx.x (xx., xx.x)
Smoking Status			
Current	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Past	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Never	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Duration of IPF (Years)			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (Q1, Q3)	xx.x (xx., xx.x)	xx.x (xx., xx.x)	xx.x (xx., xx.x)

1. Any patient whose ethnicity is Hispanic or Latino, or whose race is non-white

Baseline
Medical History

	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N=N_{EVAL}
Coronary artery disease	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Acute MI	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Valvular heart disease	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Heart failure	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Atrial fibrillation	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Intermittent claudication	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Liver disease	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Diabetes	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Lung cancer	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Other cancer	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Gastro esophageal reflux disorder	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Sleep apnea	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Asthma	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Evidence of pulmonary hypertension	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Emphysema or chronic bronchitis	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Connective tissue features	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Exposure to organic or inorganic antigens known to cause interstitial lung disease	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Clubbing	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Bilasilar, inspiratory crackles	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Jugular venous distension	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Increased P_2	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Peripheral edema	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)

Baseline
6 Minute Walk Test

Parameter Statistic	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N=N_{EVAL}
Resting SpO2 (%)			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Borg Scale Pre-Walk Rating (0-10 Range)			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Borg Scale Post-Walk Rating (0-10 Range)			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Six Minute Walk Distance (m)			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)

Baseline
Spirometry and Lung Diffusion Testing

Parameter Statistic	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N=N_{EVAL}
FEV1%			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
FVC (liters)			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
FEV_1 (liters)			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
D_LCO (mmHg)			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)

Baseline
Arterial Blood Gas and Lung Volume

Parameter Statistic	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N=N_{EVAL}
PaO_2 (mmHg)			
N (Missing)	xx (xx)		xx (xx)
Mean (SD)	x.xx (xx.x)		x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)		x.xx (x.xx, x.xx)
$PaCO_2$ (mmHg)			
N (Missing)	xx (xx)		xx (xx)
Mean (SD)	x.xx (xx.x)		x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)		x.xx (x.xx, x.xx)
SaO_2 (%)			
N (Missing)	xx (xx)		xx (xx)
Mean (SD)	x.xx (xx.x)		x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)		x.xx (x.xx, x.xx)
Total Lung Capacity (liters)			
N (Missing)	xx (xx)		xx (xx)
Mean (SD)	x.xx (xx.x)		x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)		x.xx (x.xx, x.xx)

Baseline
Other Pulmonary Factors

Parameter Statistic	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N=N_{EVAL}
Brain Natriuretic Peptide (pg/mL)			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
NYHA Heart Failure Classification			
I	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
II	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
III	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
IV	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)

Baseline
Quality of Life

Parameter Statistic	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N=N_{EVAL}
UCSD Shortness of Breath Questionnarie Total Score (0-120 Range)			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)

Baseline
Prior Medications

Medication Name	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N=N_{EVAL}
<<1st Medication Name>>	N_{MED}/N_{EVAL} (xx.x%)	N_{MED}/N_{EVAL} (xx.x%)	N_{MED}/N_{EVAL} (xx.x%)
<<2nd Medication Name>>	N_{MED}/N_{EVAL} (xx.x%)	N_{MED}/N_{EVAL} (xx.x%)	N_{MED}/N_{EVAL} (xx.x%)
<<3rd Medication Name>>	N_{MED}/N_{EVAL} (xx.x%)	N_{MED}/N_{EVAL} (xx.x%)	N_{MED}/N_{EVAL} (xx.x%)
<<4th Medication Name>>	N_{MED}/N_{EVAL} (xx.x%)	N_{MED}/N_{EVAL} (xx.x%)	N_{MED}/N_{EVAL} (xx.x%)
<<Nth Medication Name>>	N_{MED}/N_{EVAL} (xx.x%)	N_{MED}/N_{EVAL} (xx.x%)	N_{MED}/N_{EVAL} (xx.x%)

Study Status
Completed and Early Termination Patients

Study Status Reason	Period I (Week 0-12)			Period II (Week 12-24)		
	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N=N_{EVAL}	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N=N_{EVAL}
Started Study Period	N	N	N	N	N	N
Ongoing on in the study	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Completed	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
On study drug	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Removed from study drug	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Adverse Event	N	N	N	N	N	N
Withdrew consent from study drug	N	N	N	N	N	N
MD decision	N	N	N	N	N	N
Other	N	N	N	N	N	N
Unknown	N	N	N	N	N	N
Early termination	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Death	N	N	N	N	N	N
Lung Transplant	N	N	N	N	N	N
Adverse Event	N	N	N	N	N	N
Withdrew Consent	N	N	N	N	N	N
MD Decision	N	N	N	N	N	N
Lost to follow-up	N	N	N	N	N	N
Other	N	N	N	N	N	N
Unknown	N	N	N	N	N	N

Study Status
Completed and Discontinued Patients
Early Termination from Study Period I

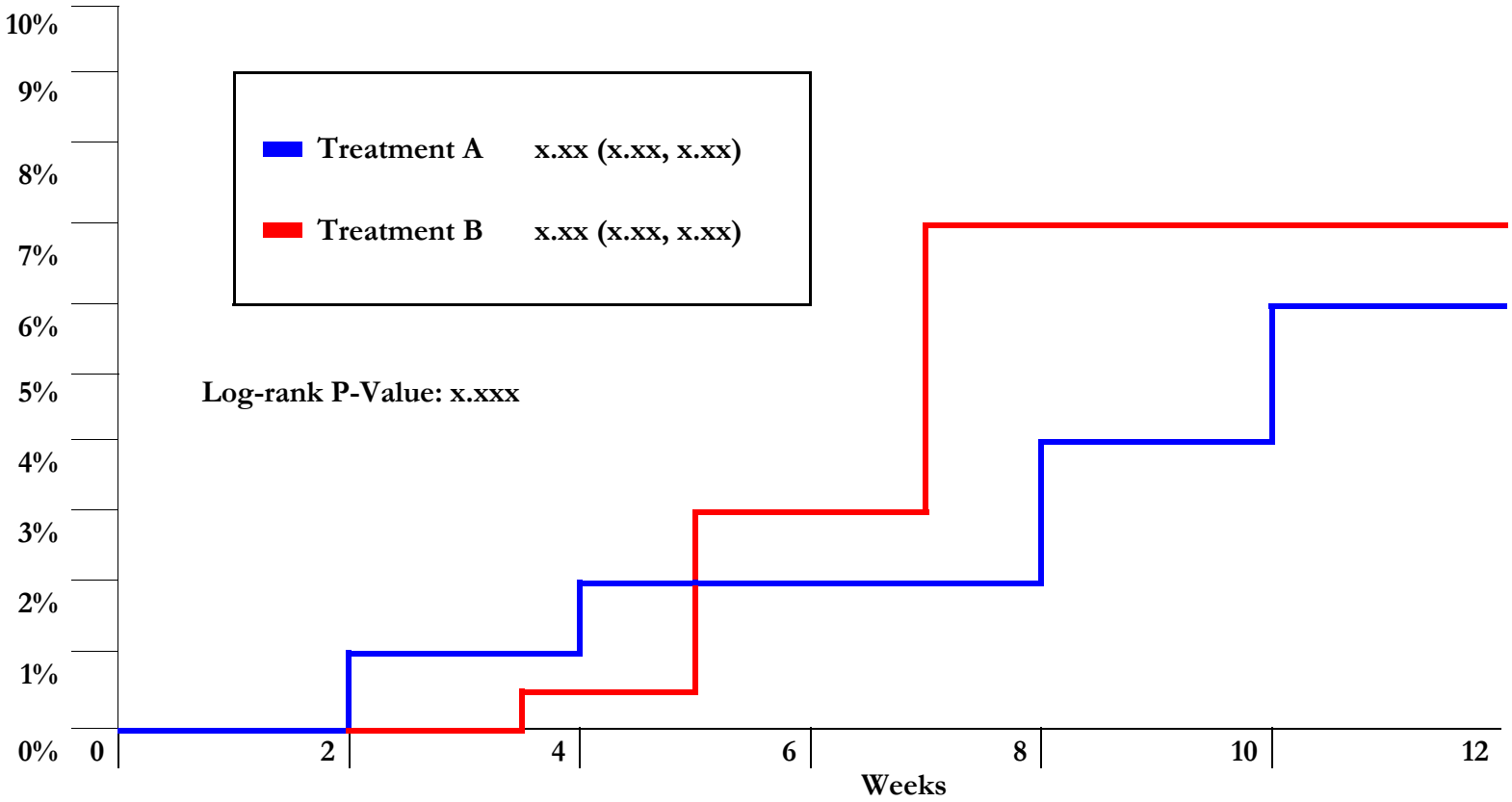
Patient ID	Investigational Site	Treatment Group	Randomization Date	Follow-up (Weeks)	Reason
XXXXXX	(001) University of California at San Francisco Medical Center	A	DDMMMYYYY	xx.x	AE/SAE
XXXXXX	(005) Tulane University Hospital	B	DDMMMYYYY	xx.x	Withdrew Consent
XXXXXX	(003) Mayo Clinic	A	DDMMMYYYY	xx.x	MD Decision
XXXXXX	(011) Weill Medical College of Cornell University	A	DDMMMYYYY	xx.x	Death
XXXXXX	(008) University of Michigan Medical Center	B	DDMMMYYYY	xx.x	Lost to Follow up
XXXXXX	(005) Tulane University Hospital	B	DDMMMYYYY	xx.x	AE/SAE
XXXXXX	(003) Mayo Clinic	A	DDMMMYYYY	xx.x	Withdrew Consent

Study Status
Completed and Discontinued Patients
Early Termination from Study Period II

Patient ID	Investigational Site	Treatment Group	Randomization Date	Follow-up (Weeks)	Reason
XXXXXX	(001) University of California at San Francisco Medical Center	A	DDMMMYYYY	xx.x	AE/SAE
XXXXXX	(005) Tulane University Hospital	B	DDMMMYYYY	xx.x	Withdrew Consent
XXXXXX	(003) Mayo Clinic	A	DDMMMYYYY	xx.x	Physician Choice
XXXXXX	(011) Weill Medical College of Cornell University	A	DDMMMYYYY	xx.x	Death
XXXXXX	(008) University of Michigan Medical Center	B	DDMMMYYYY	xx.x	Lost to Follow up
XXXXXX	(005) Tulane University Hospital	B	DDMMMYYYY	xx.x	AE/SAE
XXXXXX	(003) Mayo Clinic	A	DDMMMYYYY	xx.x	Withdrew Consent

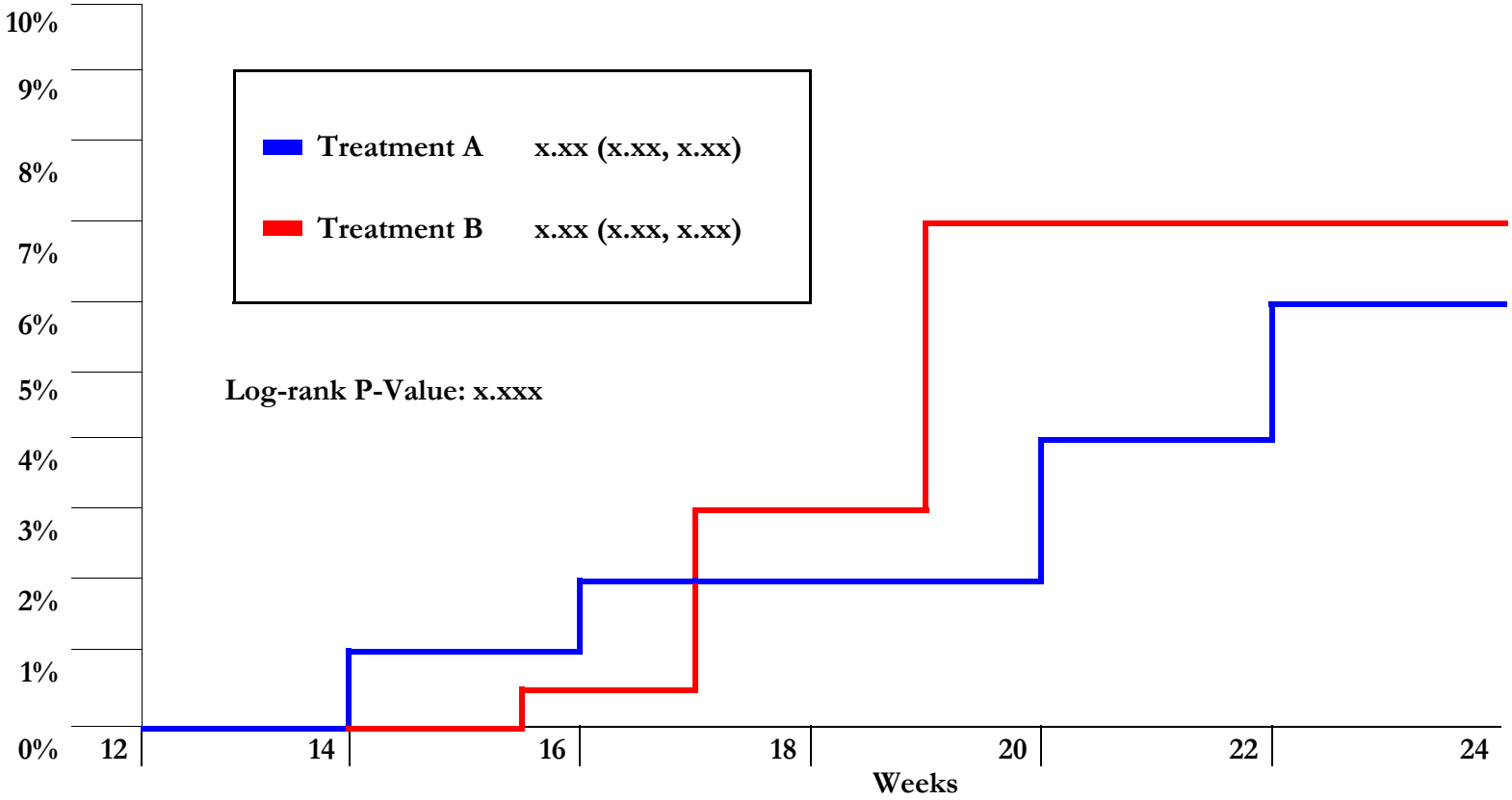
Study Status

Dropout Rate, Kaplan Meier Estimates
Period I (At 12 Weeks)



Study Status

Dropout Rate, Kaplan Meier Estimates
Period II (At 24 Weeks)



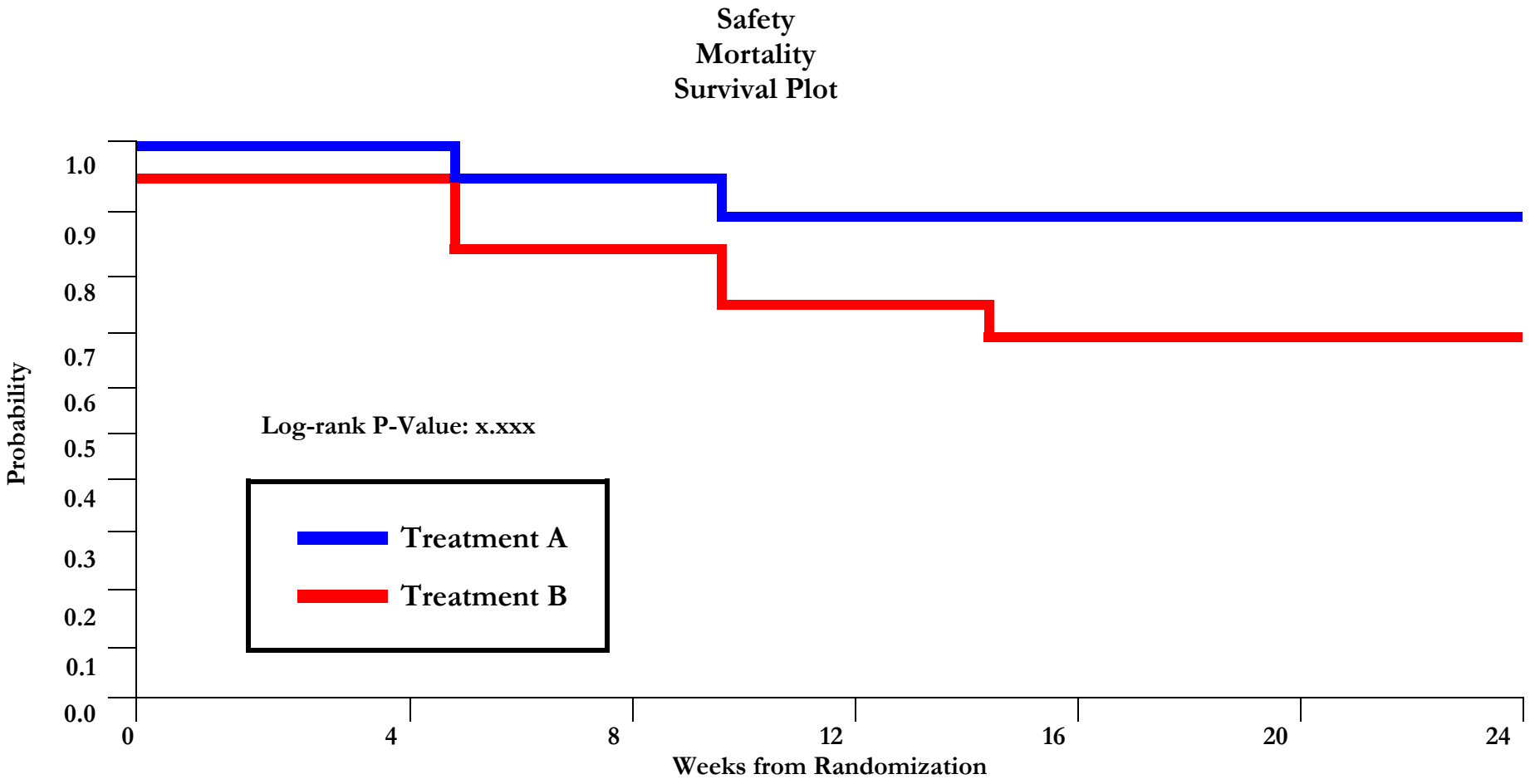
Study Status
Concomitant Medications

Medication Name	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N=N_{EVAL}
<<1st Medication Name>>	N_{MED}/N_{EVAL} (xx.x%)	N_{MED}/N_{EVAL} (xx.x%)	N_{MED}/N_{EVAL} (xx.x%)
<<2nd Medication Name>>	N_{MED}/N_{EVAL} (xx.x%)	N_{MED}/N_{EVAL} (xx.x%)	N_{MED}/N_{EVAL} (xx.x%)
<<3rd Medication Name>>	N_{MED}/N_{EVAL} (xx.x%)	N_{MED}/N_{EVAL} (xx.x%)	N_{MED}/N_{EVAL} (xx.x%)
<<4th Medication Name>>	N_{MED}/N_{EVAL} (xx.x%)	N_{MED}/N_{EVAL} (xx.x%)	N_{MED}/N_{EVAL} (xx.x%)
<<Nth Medication Name>>	N_{MED}/N_{EVAL} (xx.x%)	N_{MED}/N_{EVAL} (xx.x%)	N_{MED}/N_{EVAL} (xx.x%)

Safety
Mortality

Event	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N= N_{EVAL}	P-Value[1]
Mortality				
# of events	N	N	N	
Mortality 12 Weeks				
# of events	N/N	N/N	N/N	
Kaplan-Meier Event Rate (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	x.xxx
Mortality 24 Weeks				
# of events/# of Patients	N/N	N/N	N/N	
Kaplan-Meier Event Rate (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	x.xxx
Cause of Death				
Pulmonary	N	N	N	
Progression of IPF	N	N	N	
Embolism	N	N	N	
Lung infection	N	N	N	
Lung Cancer	N	N	N	
Other	N	N	N	
Non pulmonary	N	N	N	
Unknown	N	N	N	

1 – Log rank test


Safety
Mortality
Survival Plot
Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Log-rank P-Value: x.xxx
Treatment A
Treatment B
0
4
8
12
16
20
24
Weeks from Randomization

Safety
Pulmonary Related Events

Parameter Classification	Patient[1] Treatment A N= N_{EVAL}	 Treatment B N= N_{EVAL}	 P-Value	Event[2] Treatment A N= N_{EVAL}	 Treatment B N= N_{EVAL}
Acute Exacerbation					
Investigator	N/N (xx.x%)	N/N (xx.x%)	x.xxx	N/N (xx.x%)	N/N (xx.x%)
Adjudicated final diagnosis					
Definite acute exacerbation	N/N (xx.x%)	N/N (xx.x%)	x.xxx	N/N (xx.x%)	N/N (xx.x%)
Unclassified acute worsening	N/N (xx.x%)	N/N (xx.x%)	x.xxx	N/N (xx.x%)	N/N (xx.x%)
Other	N/N (xx.x%)	N/N (xx.x%)	x.xxx	N/N (xx.x%)	N/N (xx.x%)
FVC Drop ≥ 10% post baseline	N/N (xx.x%)	N/N (xx.x%)	x.xxx	N/N (xx.x%)	N/N (xx.x%)

1 – Patient Level – Number of Patients with one or more events
2 – Per Event - Number of events observed

Safety
Drug Related and Unexpected Serious Adverse Events

Body System Event Name	Patient[1]			Event[2]		
	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	P-Value	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	P-Value
Any Body System and Event	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
1st Body System Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
1st Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
2nd Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
…	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
Xth Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
2nd Body System Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
1st Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
2nd Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
…	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
Xth Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
Xth Body System Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
1st Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
2nd Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
…	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
Xth Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx

1 – Patient Level – Number of Patients with an Event - Summarization format N_{PAT} (xx.x%), where N_{PAT} is the number of patient with at least one SAE and xx.x% = N_{PAT} divided by the total number of randomized patients with follow-up times 100.
2 – Event Level – Total Number of Events - Summarization format N_{SAE} (xx.x%), where N_{SAE} is the number of SAEs observed and xx.x% = N_{SAE} divided by patient follow-up per 12 weeks times 100.

Safety
Drug Related and Unexpected Serious Adverse Events
Period I (0-12 Weeks)

Body System Event Name	Patient[1]			Event[2]		
	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	P-Value	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	P-Value
Any Body System and Event	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
1st Body System Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
1st Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
2nd Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
…	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
Xth Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
2nd Body System Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
1st Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
2nd Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
…	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
Xth Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
Xth Body System Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
1st Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
2nd Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
…	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
Xth Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx

1 – Patient Level – Number of Patients with an Event - Summarization format N_{PAT} (xx.x%), where N_{PAT} is the number of patient with at least one SAE and xx.x% = N_{PAT} divided by the total number of randomized patients with follow-up times 100.
2 – Event Level – Total Number of Events - Summarization format N_{SAE} (xx.x%), where N_{SAE} is the number of SAEs observed and xx.x% = N_{SAE} divided by patient follow-up per 12 weeks times 100.

Safety
Drug Related and Unexpected Serious Adverse Events
Period II (12-24 Weeks)

Body System Event Name	Patient[1]			Event[2]		
	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	P-Value	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	P-Value
Any Body System and Event	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
1st Body System Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
1st Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
2nd Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
…	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
Xth Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
2nd Body System Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
1st Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
2nd Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
…	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
Xth Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
Xth Body System Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
1st Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
2nd Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
…	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
Xth Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx

1 – Patient Level – Number of Patients with an Event - Summarization format N_{PAT} (xx.x%), where N_{PAT} is the number of patient with at least one SAE and xx.x% = N_{PAT} divided by the total number of randomized patients with follow-up times 100.
2 – Event Level – Total Number of Events - Summarization format N_{SAE} (xx.x%), where N_{SAE} is the number of SAEs observed and xx.x% = N_{SAE} divided by patient follow-up per 12 weeks times 100.

Safety
Serious Adverse Events

Body System Event Name	Patient[1]			Event[2]		
	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	P-Value	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	P-Value
Any Body System and Event	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
1st Body System Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
1st Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
2nd Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
…	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
Xth Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
2nd Body System Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
1st Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
2nd Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
…	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
Xth Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
Xth Body System Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
1st Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
2nd Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
…	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
Xth Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx

1 – Patient Level – Number of Patients with an Event - Summarization format N_{PAT} (xx.x%), where N_{PAT} is the number of patient with at least one SAE and xx.x% = N_{PAT} divided by the total number of randomized patients with follow-up times 100.
2 – Event Level – Total Number of Events - Summarization format N_{SAE} (xx.x%), where N_{SAE} is the number of SAEs observed and xx.x% = N_{SAE} divided by patient follow-up per 12 weeks times 100.

Safety
Serious Adverse Events
Period I (0-12 Weeks)

Body System Event Name	Patient[1]			Event[2]		
	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	P-Value	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	P-Value
Any Body System and Event	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
1st Body System Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
1st Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
2nd Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
…	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
Xth Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
2nd Body System Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
1st Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
2nd Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
…	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
Xth Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
Xth Body System Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
1st Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
2nd Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
…	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
Xth Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx

1 – Patient Level – Number of Patients with an Event - Summarization format N_{PAT} (xx.x%), where N_{PAT} is the number of patient with at least one SAE and xx.x% = N_{PAT} divided by the total number of randomized patients with follow-up times 100.
2 – Event Level – Total Number of Events - Summarization format N_{SAE} (xx.x%), where N_{SAE} is the number of SAEs observed and xx.x% = N_{SAE} divided by patient follow-up per 12 weeks times 100.

Safety
Serious Adverse Events
Period II (12-24 Weeks)

Body System Event Name	Patient[1]			Event[2]		
	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	P-Value	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	P-Value
Any Body System and Event	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
1st Body System Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
1st Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
2nd Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
…	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
Xth Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
2nd Body System Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
1st Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
2nd Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
…	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
Xth Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
Xth Body System Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
1st Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
2nd Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
…	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx
Xth Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{SAE} (xx.x%)	N_{SAE} (xx.x%)	x.xxx

1 – Patient Level – Number of Patients with an Event - Summarization format N_{PAT} (xx.x%), where N_{PAT} is the number of patient with at least one SAE and xx.x% = N_{PAT} divided by the total number of randomized patients with follow-up times 100.
2 – Event Level – Total Number of Events - Summarization format N_{SAE} (xx.x%), where N_{SAE} is the number of SAEs observed and xx.x% = N_{SAE} divided by patient follow-up per 12 weeks times 100.

Safety
Adverse Events

Body System Event Name	Patient[1]			Event[2]		
	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	P-Value	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	P-Value
Any Body System and Event	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
1st Body System Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
1st Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
2nd Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
…	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
Xth Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
2nd Body System Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
1st Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
2nd Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
…	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
Xth Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
Xth Body System Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
1st Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
2nd Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
…	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
Xth Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx

1 – Patient Level – Number of Patients with an Event - Summarization format N_{PAT} (xx.x%), where N_{PAT} is the number of patient with at least one AE and xx.x% = N_{PAT} divided by the total number of randomized patients with follow-up times 100.
2 – Event Level – Total Number of Events - Summarization format N_{AE} (xx.x%), where N_{AE} is the number of AEs observed and xx.x% = N_{AE} divided by patient follow-up per 12 weeks times 100.

Safety
Adverse Events
Period I (0-12 Weeks)

Body System Event Name	Patient[1]			Event[2]		
	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	P-Value	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	P-Value
Any Body System and Event	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
1st Body System Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
1st Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
2nd Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
…	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
Xth Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
2nd Body System Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
1st Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
2nd Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
…	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
Xth Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
Xth Body System Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
1st Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
2nd Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
…	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
Xth Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx

1 – Patient Level – Number of Patients with an Event - Summarization format N_{PAT} (xx.x%), where N_{PAT} is the number of patient with at least one AE and xx.x% = N_{PAT} divided by the total number of randomized patients with follow-up times 100.
2 – Event Level – Total Number of Events - Summarization format N_{AE} (xx.x%), where N_{AE} is the number of AEs observed and xx.x% = N_{AE} divided by patient follow-up per 12 weeks times 100.

Safety
Adverse Events
Period II (12-24 Weeks)

Body System Event Name	Patient[1]			Event[2]		
	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	P-Value	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	P-Value
Any Body System and Event	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
1st Body System Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
1st Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
2nd Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
…	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
Xth Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
2nd Body System Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
1st Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
2nd Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
…	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
Xth Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
Xth Body System Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
1st Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
2nd Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
…	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx
Xth Event Name	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)	x.xxx	N_{AE} (xx.x%)	N_{AE} (xx.x%)	x.xxx

1 – Patient Level – Number of Patients with an Event - Summarization format N_{PAT} (xx.x%), where N_{PAT} is the number of patient with at least one AE and xx.x% = N_{PAT} divided by the total number of randomized patients with follow-up times 100.
2 – Event Level – Total Number of Events - Summarization format N_{AE} (xx.x%), where N_{AE} is the number of AEs observed and xx.x% = N_{AE} divided by patient follow-up per 12 weeks times 100.

Safety
Clinical Laboratory Data
Out of Range Values

Parameter Time Period	Patient[1] Treatment A N= N_{EVAL}	 Treatment B N= N_{EVAL}	 P-Value	Event[2] Treatment A N= N_{EVAL}	 Treatment B N= N_{EVAL}
ALT					
Baseline			x.xxx		
Normal	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Below	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Above	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Period I			x.xxx		
Normal	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Below	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Above	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Period II			x.xxx		
Normal	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Below	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Above	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
AST					
Baseline			x.xxx		
Normal	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Below	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Above	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Period I			x.xxx		
Normal	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Below	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Above	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Period II			x.xxx		
Normal	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Below	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Above	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}

Safety
Clinical Laboratory Data
Out of Range Values

Parameter Time Period	Patient[1] Treatment A N= N_{EVAL}	 Treatment B N= N_{EVAL}	 P-Value	Event[2] Treatment A N= N_{EVAL}	 Treatment B N= N_{EVAL}
Total Bilirubin					
Baseline			x.xxx		
Normal	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Below	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Above	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Period I			x.xxx		
Normal	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Below	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Above	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Period II			x.xxx		
Normal	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Below	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Above	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Creatninine					
Baseline			x.xxx		
Normal	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Below	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Above	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Period I			x.xxx		
Normal	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Below	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Above	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Period II			x.xxx		
Normal	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Below	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Above	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Hemoglobin					

Safety
Clinical Laboratory Data
Out of Range Values

Parameter Time Period	Patient[1] Treatment A N= N_{EVAL}	 Treatment B N= N_{EVAL}	 P-Value	Event[2] Treatment A N= N_{EVAL}	 Treatment B N= N_{EVAL}
Baseline			x.xxx		
Normal	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Below	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Above	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Period I			x.xxx		
Normal	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Below	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Above	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Period II			x.xxx		
Normal	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Below	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Above	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
WBC					
Baseline			x.xxx		
Normal	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Below	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Above	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Period I			x.xxx		
Normal	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Below	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Above	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Period II			x.xxx		
Normal	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Below	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}
Above	N_{PAT} (xx.x%)	N_{PAT} (xx.x%)		N_{LAB}	N_{LAB}

1 – Patient Level – Number of Patients with an Event - Summarization format N_{PAT} (xx.x%), where N_{PAT} is the number of patient with at least one classified lab value and xx.x% = N_{PAT} divided by the total number of patients with a lab value present times 100.

Safety
Clinical Laboratory Data
Out of Range Values

Parameter Time Period	Patient[1] Treatment A N= N_{EVAL}	 Treatment B N= N_{EVAL}	 P-Value	Event[2] Treatment A N= N_{EVAL}	 Treatment B N= N_{EVAL}

2 – Per Event - N_{LAB} is the number of classified lab values

Safety
Arterial Blood Gas
Descriptive Summary

Parameter Visit Statistic	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N= N_{EVAL}	P-Value
PaO_2 (mmHg)				
Baseline				x.xxx
N (Missing)	xx (xx)	xx (xx)	xx (xx)	
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)	
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	
Week 12				x.xxx
N (Missing)	xx (xx)	xx (xx)	xx (xx)	
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)	
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	
Week 24				x.xxx
N (Missing)	xx (xx)	xx (xx)	xx (xx)	
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)	
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	
SaO_2 (%)				
Baseline				x.xxx
N (Missing)	xx (xx)	xx (xx)	xx (xx)	
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)	
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	
Week 12				x.xxx
N (Missing)	xx (xx)	xx (xx)	xx (xx)	
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)	
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	
Week 24				x.xxx
N (Missing)	xx (xx)	xx (xx)	xx (xx)	
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)	
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	

Safety
Arterial Blood Gas
Descriptive Summary

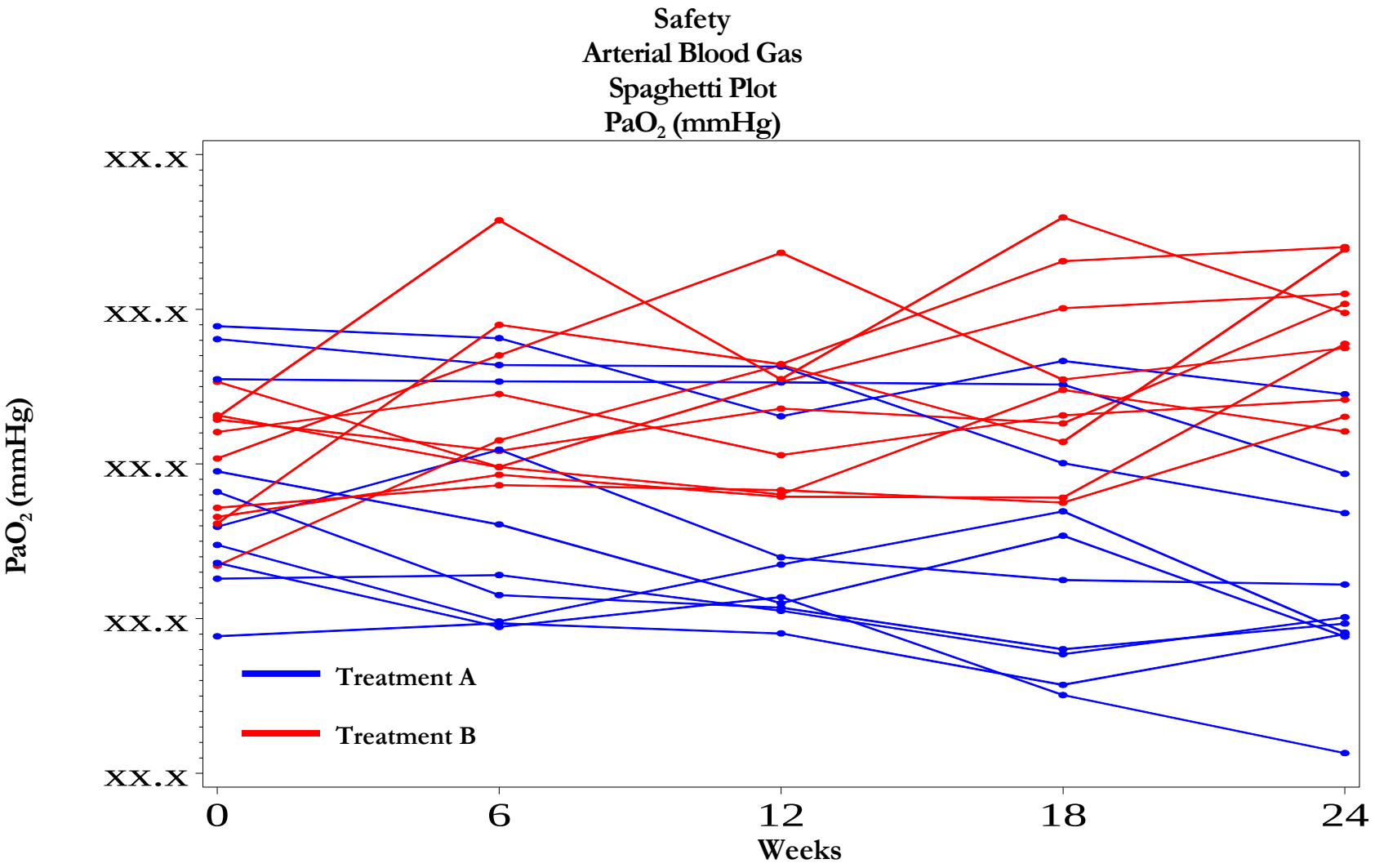
Parameter Visit Statistic	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N= N_{EVAL}	P-Value
A-a Gradient (mmHg)				
Baseline				x.xxx
N (Missing)	xx (xx)	xx (xx)	xx (xx)	
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)	
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	
Week 12				x.xxx
N (Missing)	xx (xx)	xx (xx)	xx (xx)	
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)	
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	
Week 24				x.xxx
N (Missing)	xx (xx)	xx (xx)	xx (xx)	
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)	
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	

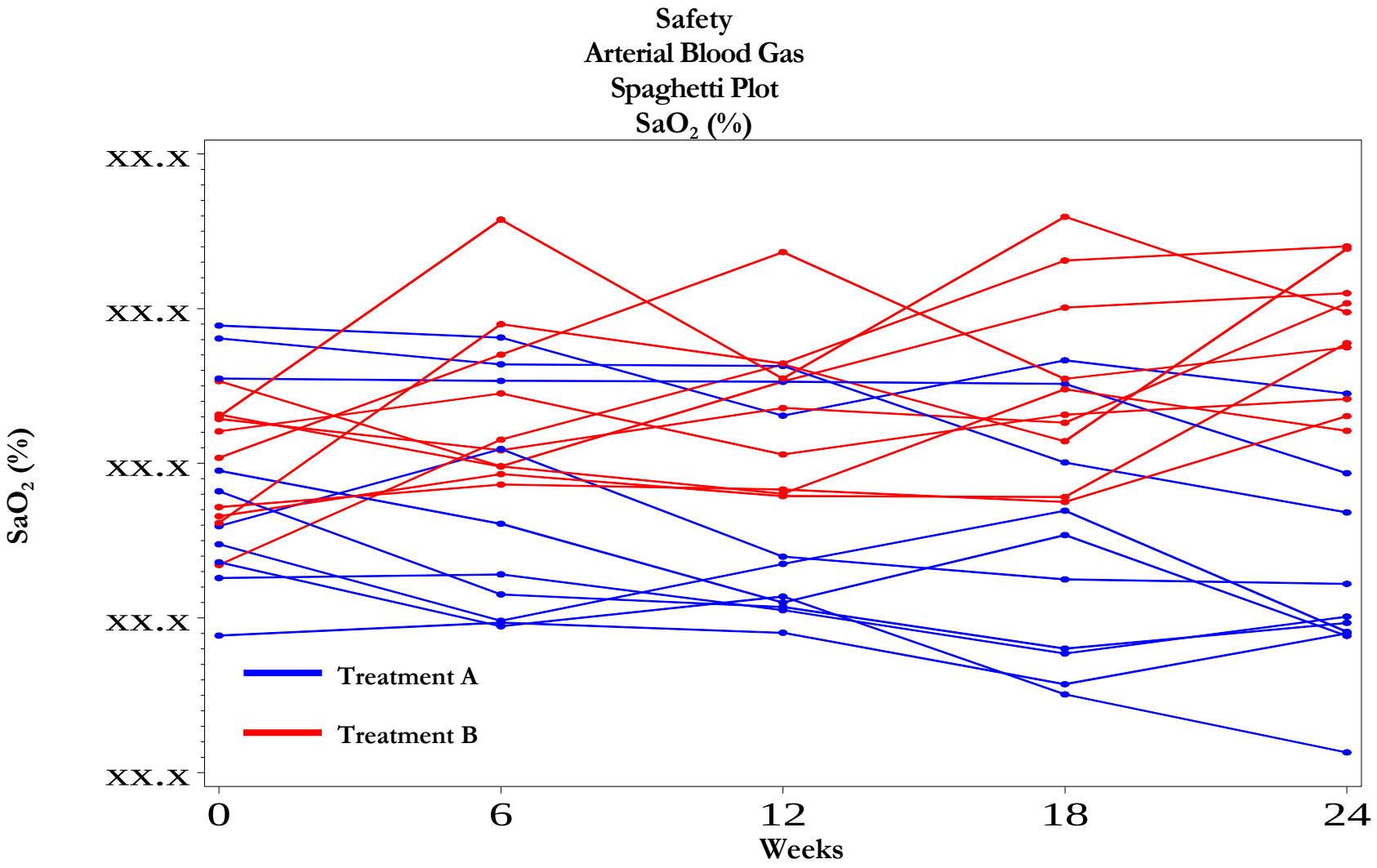
Safety
Arterial Blood Gas
Change from Baseline Summary

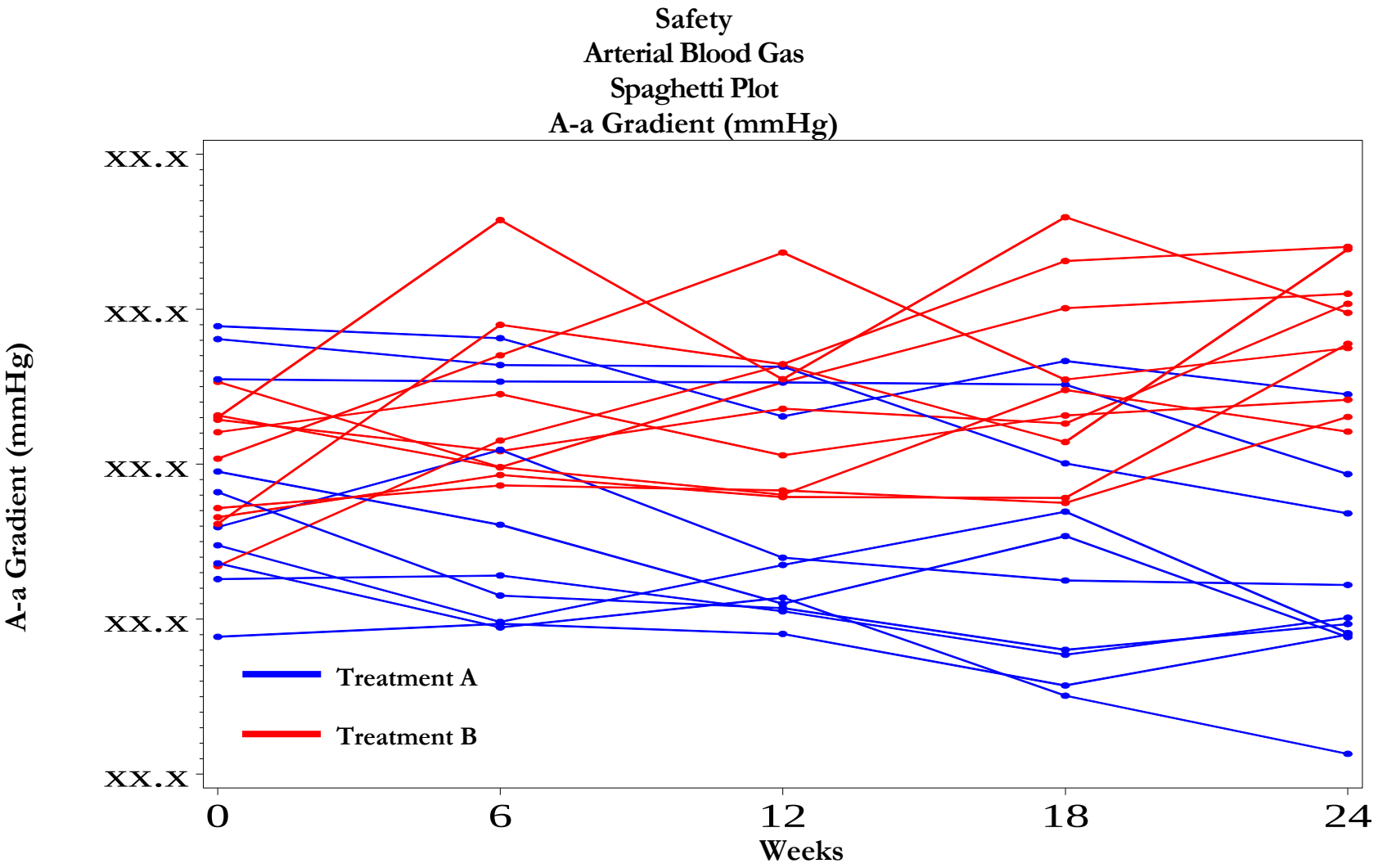
Parameter Visit Statistic	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N= N_{EVAL}	P-Value
PaO_2 (mmHg)				
Week 12 Change from baseline				x.xxx
N (Missing)	xx (xx)	xx (xx)	xx (xx)	
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)	
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	
Week 24 Change from baseline				x.xxx
N (Missing)	xx (xx)	xx (xx)	xx (xx)	
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)	
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	
SaO_2 (%)				
Week 12 Change from baseline				x.xxx
N (Missing)	xx (xx)	xx (xx)	xx (xx)	
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)	
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	
Week 24 Change from baseline				x.xxx
N (Missing)	xx (xx)	xx (xx)	xx (xx)	
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)	
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	
A-a Gradient (mmHg)				
Week 12 Change from baseline				x.xxx
N (Missing)	xx (xx)	xx (xx)	xx (xx)	
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)	
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	
Week 24 Change from baseline				x.xxx
N (Missing)	xx (xx)	xx (xx)	xx (xx)	

Safety
Arterial Blood Gas
Change from Baseline Summary

Parameter Visit Statistic	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N= N_{EVAL}	P-Value
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)	
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	


Safety
Arterial Blood Gas
Spaghetti Plot
PaO2 (mmHg)
PaO2 (mmHg)
XX.X
XX.X
XX.X
XX.X
XX.X
Treatment A
Treatment B
0
6
12
18
24
Weeks

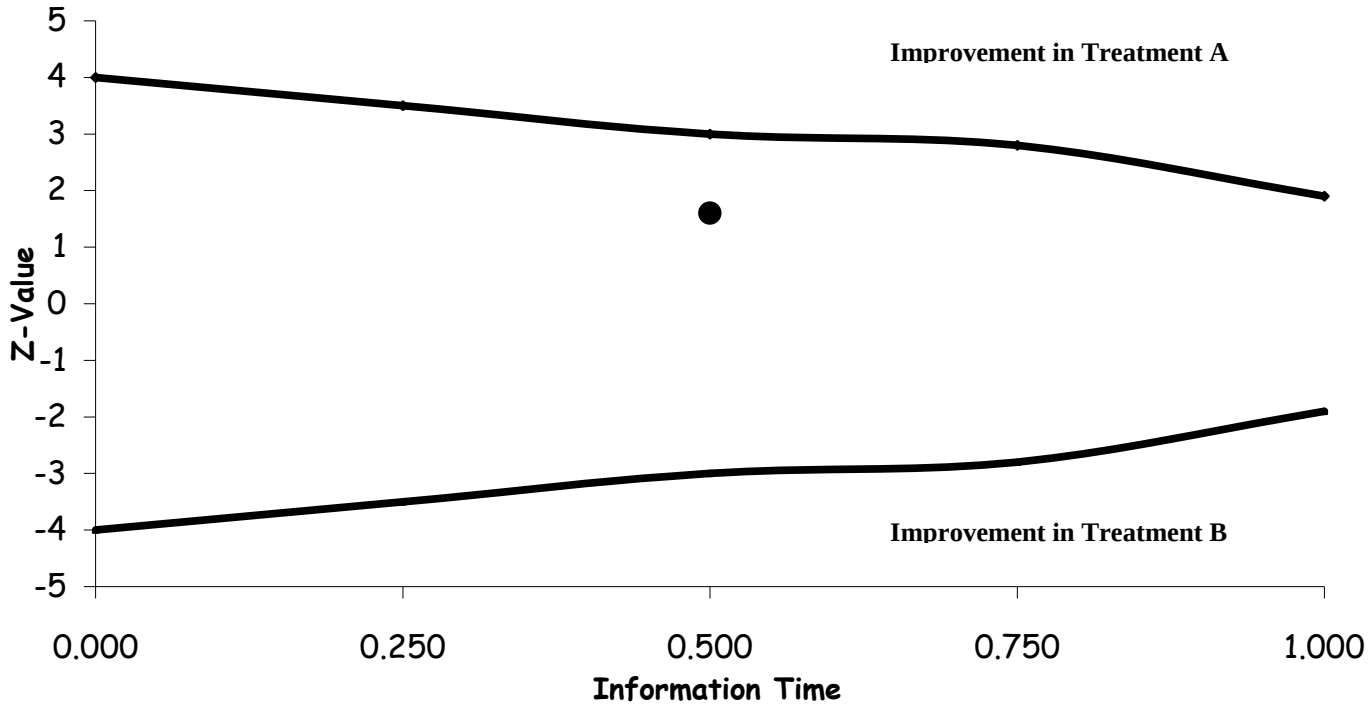

Safety
Arterial Blood Gas
Spaghetti Plot
SaO2 (%)
SaO2 (%)
XX.X
XX.X
XX.X
XX.X
XX.X
Treatment A
Treatment B
0
6
12
18
24
Weeks


Safety
Arterial Blood Gas
Spaghetti Plot
A-a Gradient (mmHg)
A-a Gradient (mmHg)
XX.X
XX.X
XX.X
XX.X
XX.X
Treatment A
Treatment B
0
6
12
18
24
Weeks

Safety
Arterial Blood Gas
Longitudinal Analysis

Parameter	Slope Estimate with 95% CI		Difference of A vs. B		
Time Interval	Treatment A	Treatment B	Estimate with 95% CI	z Value	P-Value
PaO_2 (mmHg)					
Week 0-6	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 0-12	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 12-24	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 0-24	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
SaO_2 (%)					
Week 0-6	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 0-12	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 12-24	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 0-24	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
A-a Gradient (mmHg)					
Week 0-6	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 0-12	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 12-24	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 0-24	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx

Efficacy
Primary Endpoint Evaluation with Monitoring Boundaries
20+% Improvement in 6 Minute Walk Distance (Week 0-12)



Proportion Improved with 95% CI		Odds Ratio of A vs. B		
Treatment A	**Treatment B**	**Estimate with 95% CI**	**Chi-Sq Value**	**P-Value**
xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx

Efficacy
20+% Improvement in 6 Minute Walk Distance per Visit

	Proportion Improved with 95% CI		Odds Ratio of A vs. B		
Visit	**Treatment A**	**Treatment B**	**Estimate with 95% CI**	**Chi-Sq Value**	**P-Value**
Week 6	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 12	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 18	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 24	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx

Efficacy
6 Minute Walk Distance
Descriptive Summary

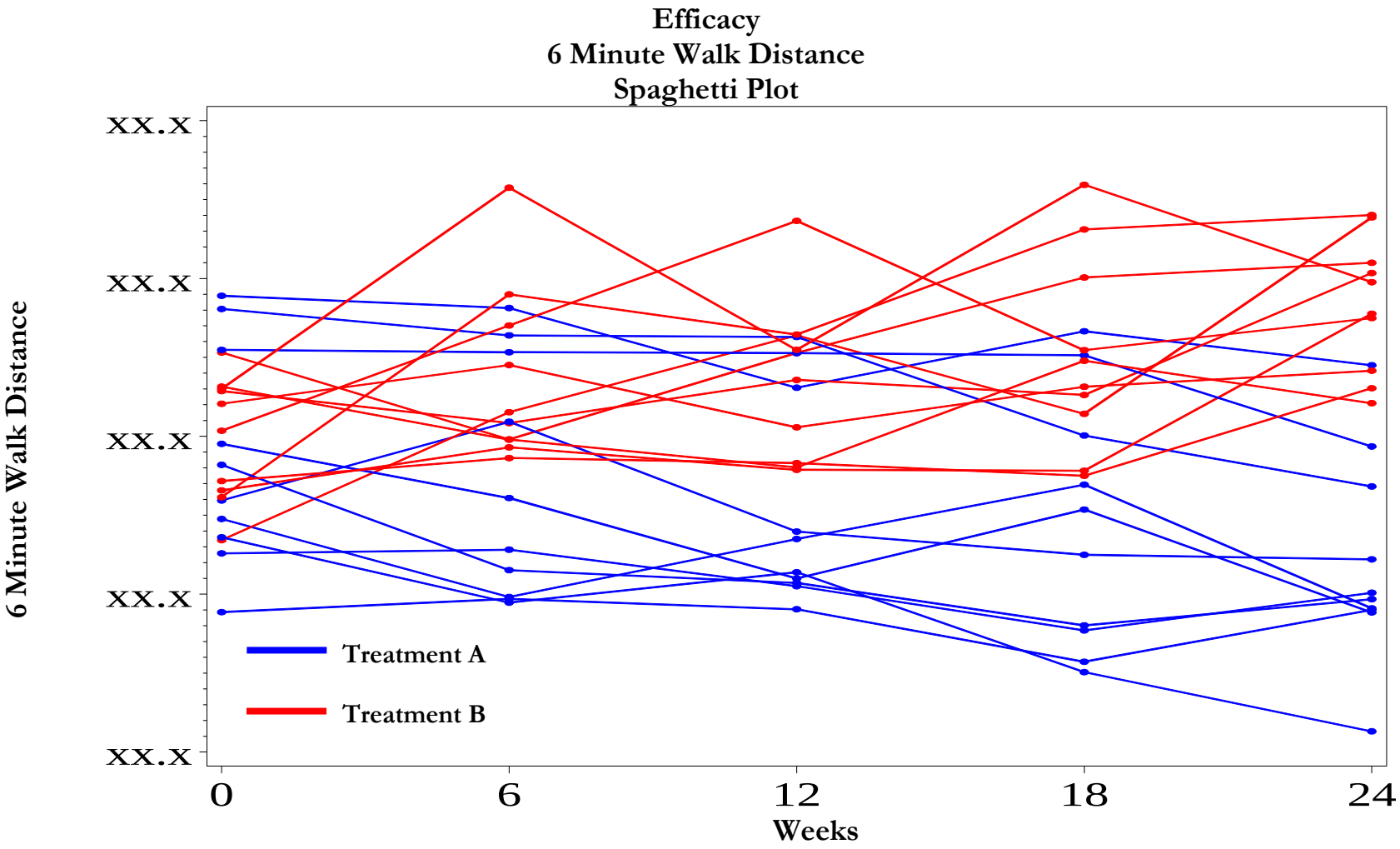
Parameter Visit Statistic	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N= N_{EVAL}
Six Minute Walk Distance (m)			
Screening			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 6			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 12			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 18			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 24			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)

Efficacy
6 Minute Walk Distance
Change from Baseline Summary

Parameter Visit Statistic	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N= N_{EVAL}
Six Minute Walk Distance (m)			
Week 6 Change from baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
5+% Improvement	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
10+% Improvement	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
20+% Improvement	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
30+% Improvement	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Week 12 Change from baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
5+% Improvement	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
10+% Improvement	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
20+% Improvement	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
30+% Improvement	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Week 18 Change from baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
5+% Improvement	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
10+% Improvement	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
20+% Improvement	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
30+% Improvement	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Week 24 Change from baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)

Efficacy
6 Minute Walk Distance
Change from Baseline Summary

Parameter Visit Statistic	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N= N_{EVAL}
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
5+% Improvement	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
10+% Improvement	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
20+% Improvement	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
30+% Improvement	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)


Efficacy
6 Minute Walk Distance
Spaghetti Plot
6 Minute Walk Distance
xx.x
xx.x
xx.x
xx.x
xx.x
Treatment A
Treatment B
0
6
12
18
24
Weeks

Efficacy
6 Minute Walk Distance
Longitudinal Analysis

Parameter	Slope Estimate with 95% CI		Difference of A vs. B		
Time Interval	Treatment A	Treatment B	Estimate with 95% CI	z Value	P-Value
6 Minute Walk Distance					
Week 0-6	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 0-12	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 12-24	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 0-24	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx

Efficacy
Measures Related to 6 Minute Walk Distance
Descriptive Summary

Parameter Visit Statistic	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N= N_{EVAL}
Borg Scale Pre-Walk Rating			
Baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)
Week 6			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)
Week 12			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)
Week 18			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)
Week 24			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)
Borg Scale Post-Walk Rating			
Baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)

Efficacy
Measures Related to 6 Minute Walk Distance
Descriptive Summary

Parameter Visit Statistic	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N= N_{EVAL}
Week 6			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)
Week 12			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)
Week 18			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)
Week 24			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)
Resting SpO2 (%)			
Baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)
Week 6			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)
Week 12			
N (Missing)	xx (xx)	xx (xx)	xx (xx)

Efficacy
Measures Related to 6 Minute Walk Distance
Descriptive Summary

Parameter Visit Statistic	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N= N_{EVAL}
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)
Week 18			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)
Week 24			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)

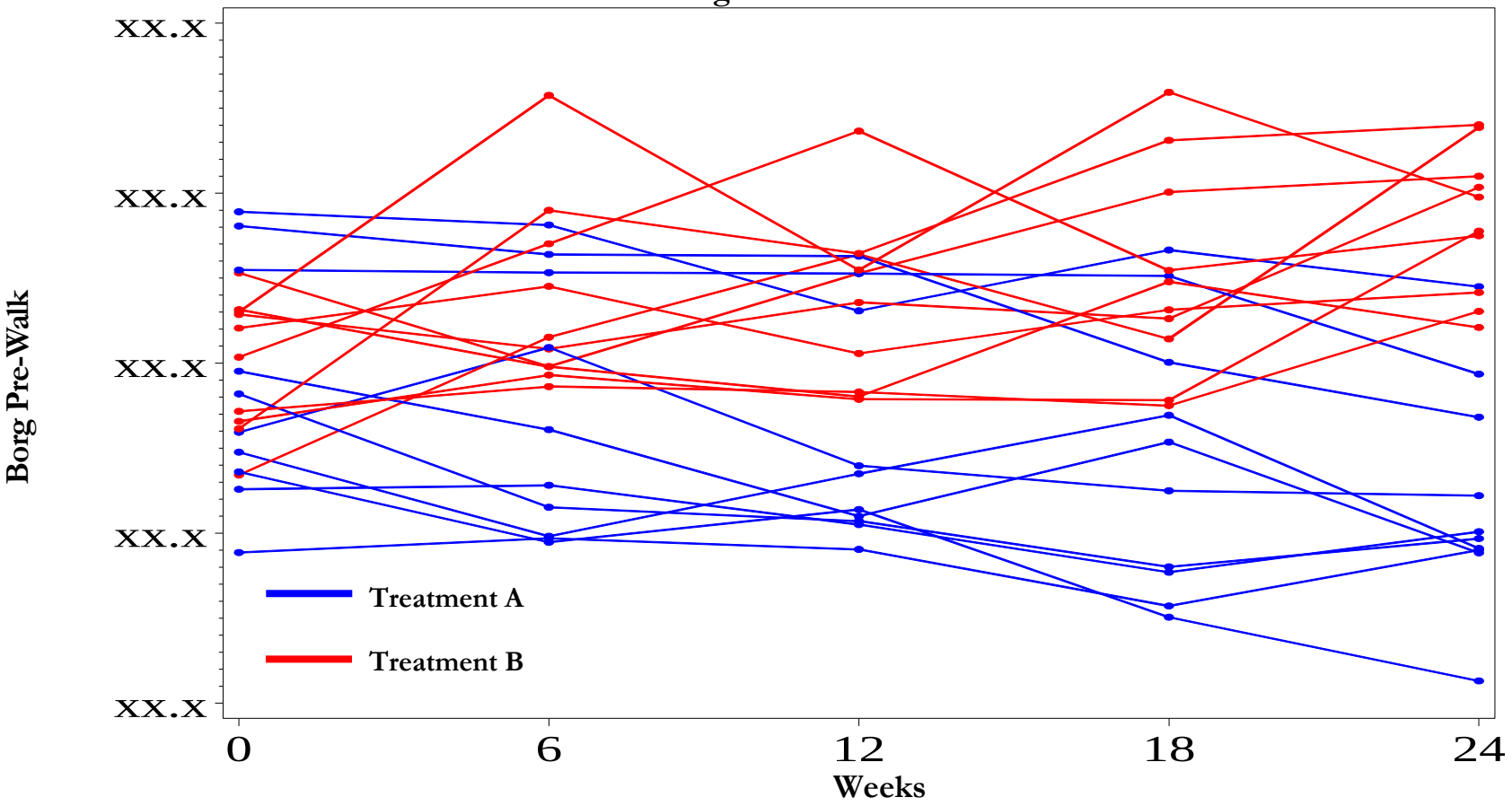
Efficacy
Measures Related to 6 Minute Walk Distance
Change from Baseline Summary

Parameter Visit Statistic	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N= N_{EVAL}
Borg Scale Pre-Walk Rating			
Week 6 Change from baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)
…	…	…	…
Week 24 Change from baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)
Borg Scale Post-Walk Rating			
Week 6 Change from baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)
…	…	…	…
Week 24 Change from baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)
Resting SpO_2 (%)			
Week 6 Change from baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)

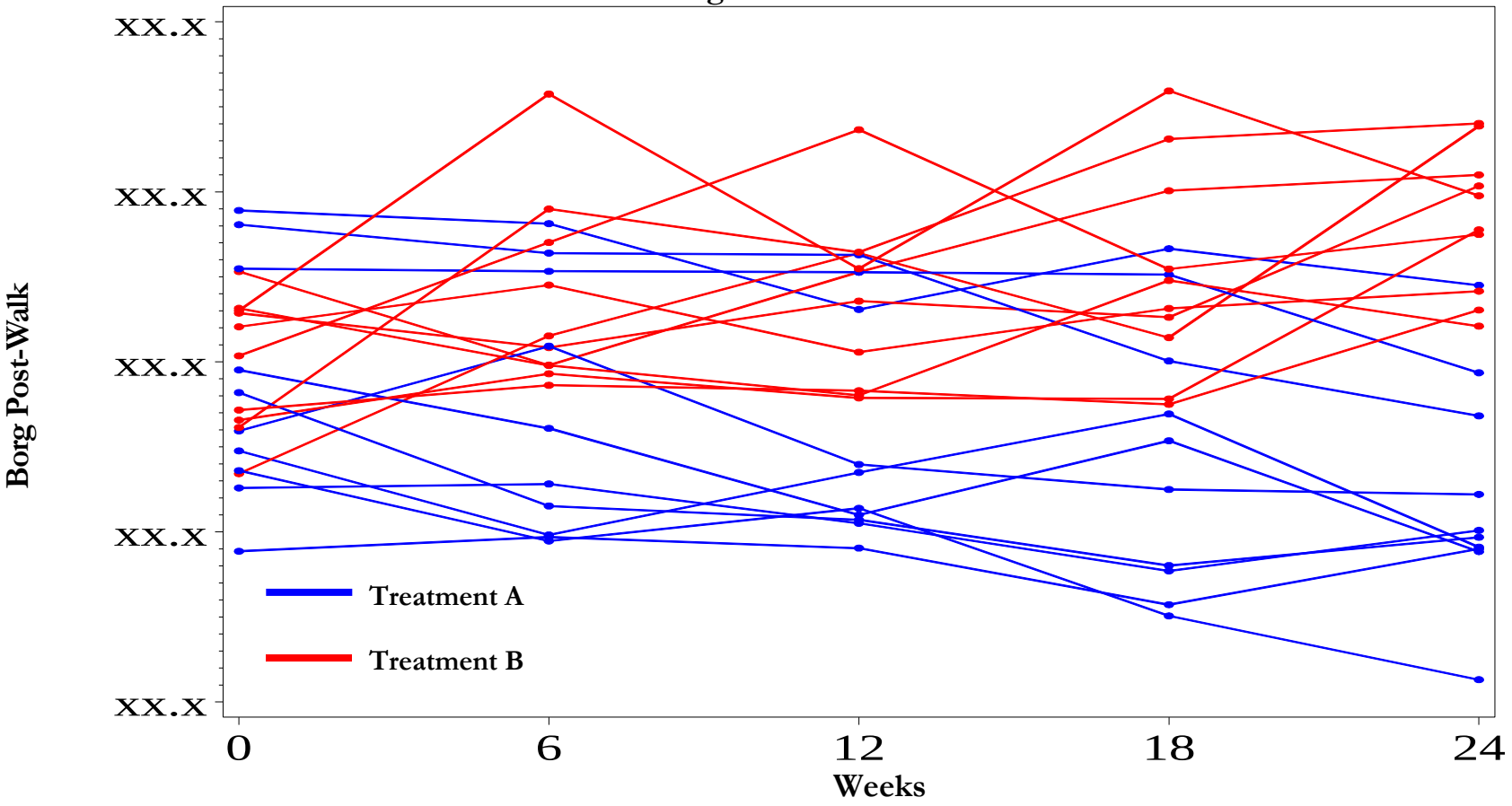
Efficacy
Measures Related to 6 Minute Walk Distance
Change from Baseline Summary

Parameter Visit Statistic	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N= N_{EVAL}
…	…	…	…
Week 24 Change from baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)
Median (Q1, Q3)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)

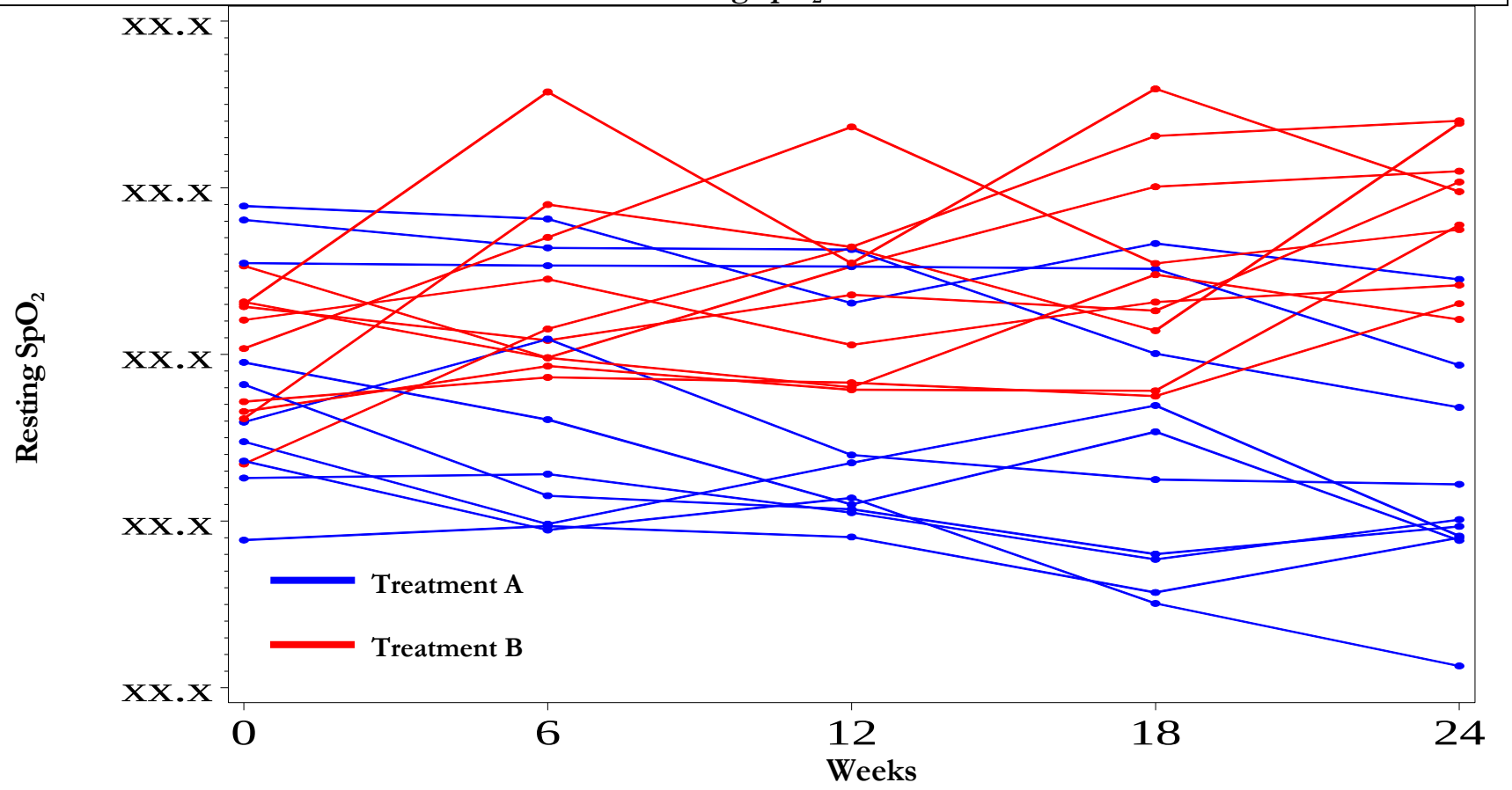
Efficacy
Measures Related to 6 Minute Walk Distance
Spaghetti Plot
Borg Pre-Walk



Efficacy
Measures Related to 6 Minute Walk Distance
Spaghetti Plot
Borg Post-Walk



Efficacy
Measures Related to 6 Minute Walk Distance
Spaghetti Plot
Resting SpO_2



Efficacy
Measures Related to 6 Minute Walk Distance
Longitudinal Analysis

Parameter	Slope Estimate with 95% CI		Difference of A vs. B		
Time Interval	Treatment A	Treatment B	Estimate with 95% CI	z Value	P-Value
6 Minute Walk Distance					
Week 0-6	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 0-12	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 12-24	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 0-24	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Borg Scale Post-Walk Rating					
Week 0-6	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 0-12	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 12-24	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 0-24	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Resting SpO_2 (%)					
Week 0-6	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 0-12	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 12-24	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 0-24	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx

Secondary Endpoints
Spirometry
Descriptive Summary

Parameter Visit Statistic	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N= N_{EVAL}
FVC (liters)			
Baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 6			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 12			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 18			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 24			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
FEV_1 (liters)			
Baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)

Secondary Endpoints
Spirometry
Descriptive Summary

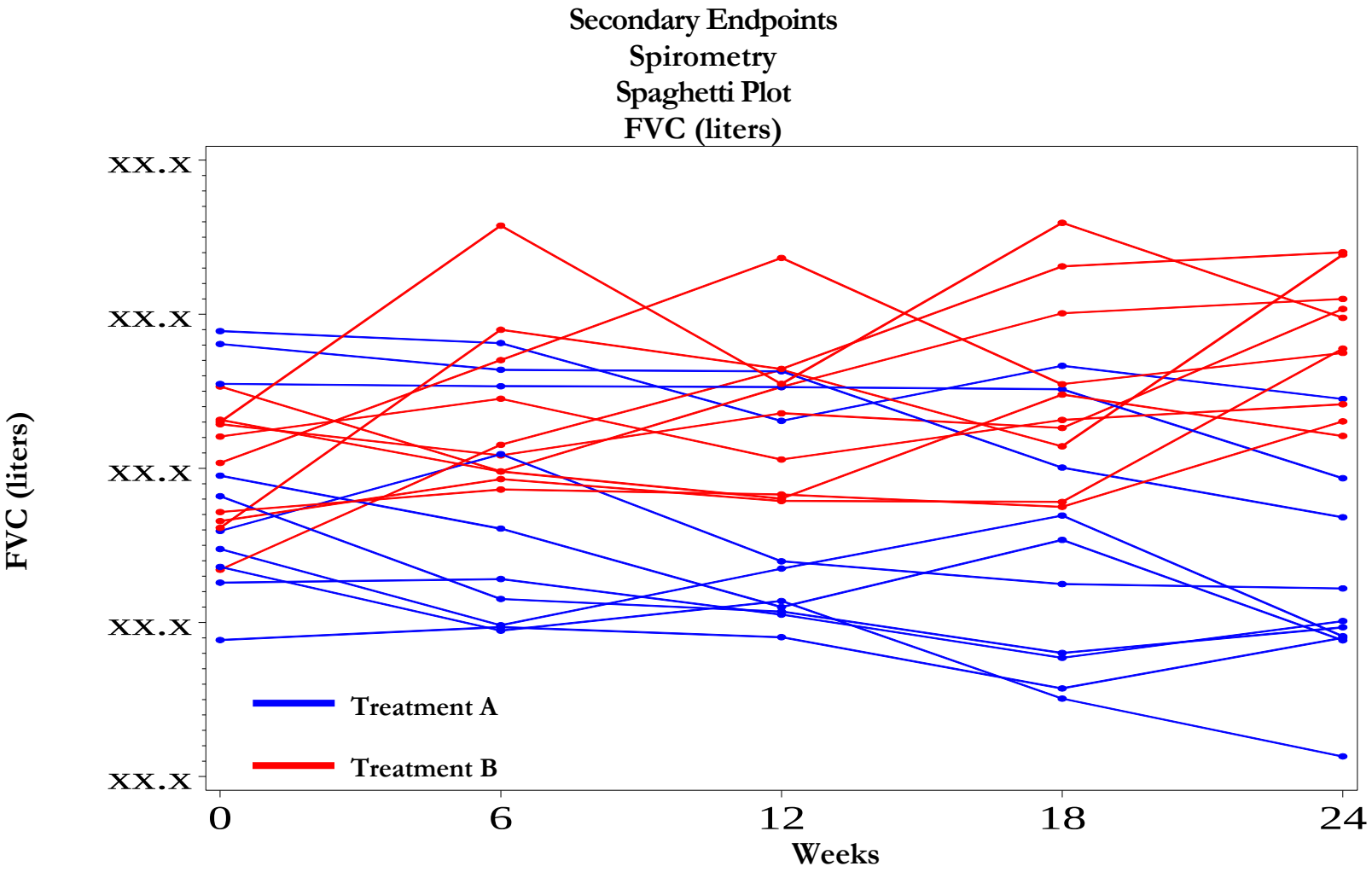
Parameter Visit Statistic	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N= N_{EVAL}
Week 6			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 12			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 18			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 24			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)

Secondary Endpoints
Spirometry
Change from Baseline Summary

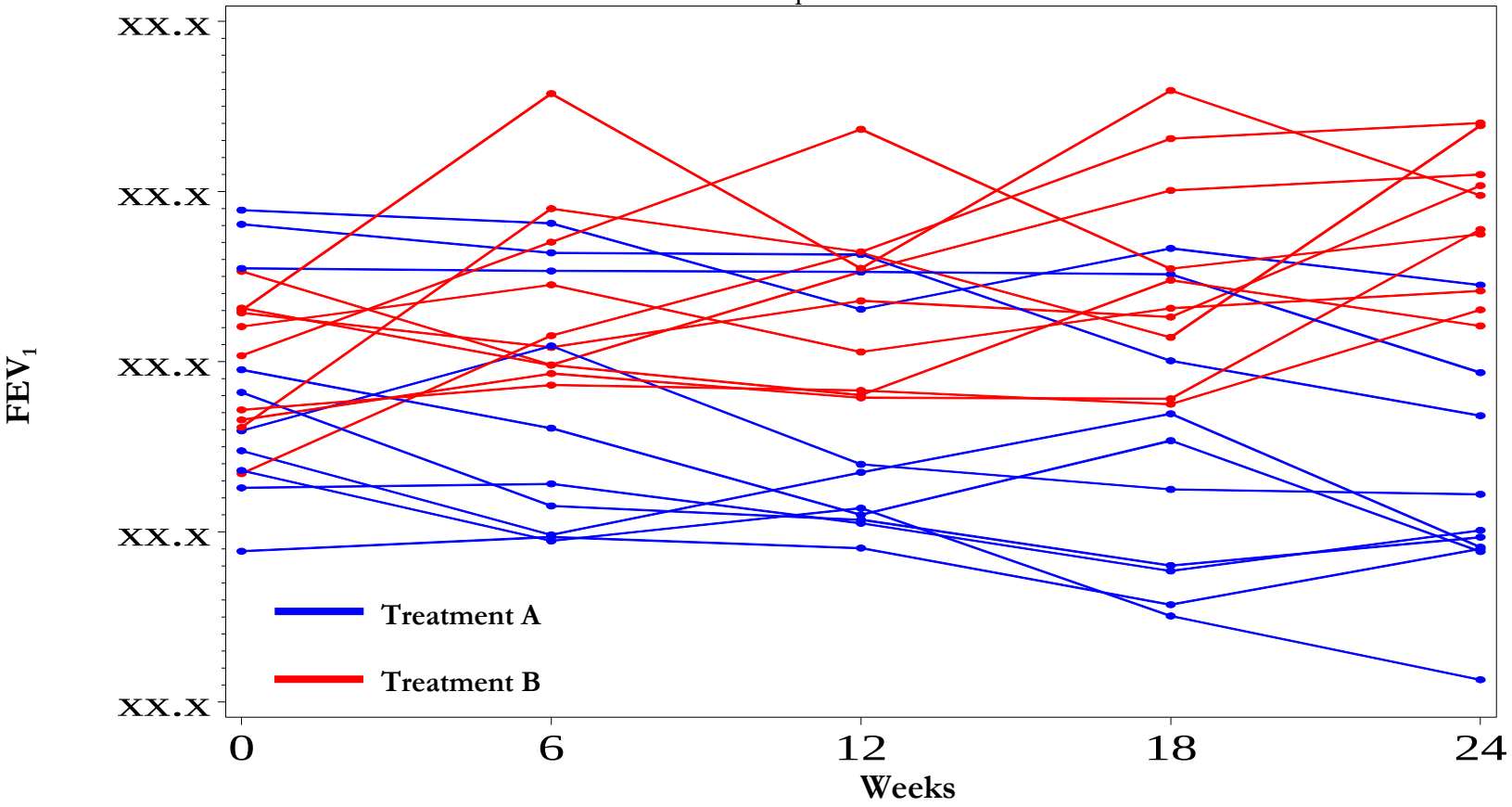
Parameter Visit Statistic	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N= N_{EVAL}
FVC (liters)			
Week 6 Change from baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 12 Change from baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 18 Change from baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 24 Change from baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
FEV_1 (liters)			
Week 6 Change from baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 12 Change from baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)

Secondary Endpoints
Spirometry
Change from Baseline Summary

Parameter Visit Statistic	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N= N_{EVAL}
Week 18 Change from baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 24 Change from baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)


Secondary Endpoints
Spirometry
Spaghetti Plot
FVC (liters)
FVC (liters)
xx.x
xx.x
xx.x
xx.x
xx.x
Treatment A
Treatment B
0
6
12
18
24
Weeks

Secondary Endpoints
Spirometry
Spaghetti Plot
FEV_1



Secondary Endpoints
Spirometry
Longitudinal Analysis

Parameter	Slope Estimate with 95% CI		Difference of A vs. B		
Time Interval	Treatment A	Treatment B	Estimate with 95% CI	z Value	P-Value
FVC (liters)					
Week 0-6	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 0-12	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 12-24	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 0-24	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
FEV_1 (liters)					
Week 0-6	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 0-12	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 12-24	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 0-24	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx

Secondary Endpoints
Lung Diffusion Testing
Descriptive Summary

Parameter Visit Statistic	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N= N_{EVAL}
D_LCO (mmHg)			
Baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 6			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 12			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 18			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 24			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)

Secondary Endpoints
Lung Diffusion Testing
Change from Baseline Summary

Parameter Visit Statistic	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N= N_{EVAL}
D_LCO (mmHg)			
Week 6 Change from baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 12 Change from baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 18 Change from baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 24 Change from baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)

Secondary Endpoints
Lung Diffusion Testing
Longitudinal Analysis

Parameter	Slope Estimate with 95% CI		Difference of A vs. B		
Time Interval	Treatment A	Treatment B	Estimate with 95% CI	z Value	P-Value
D_LCO (mmHg)					
Week 0-6	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 0-12	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 12-24	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 0-24	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx

Secondary Endpoints
Cardiac Function
Descriptive Summary

Parameter Visit Statistic	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N= N_{EVAL}
Brain Natriuretic Peptide (pg/mL)			
Baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 6			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 12			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 18			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 24			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
NYHA Heart Failure Classification			
Baseline			
I	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
II	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
III	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)

Secondary Endpoints
Cardiac Function
Descriptive Summary

Parameter Visit Statistic	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N= N_{EVAL}
IV	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Week 6			
I	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
II	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
III	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
IV	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Week 12			
I	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
II	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
III	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
IV	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Week 18			
I	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
II	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
III	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
IV	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Week 24			
I	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
II	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
III	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
IV	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)

Secondary Endpoints
Cardiac Function
Change from Baseline Summary

Parameter Visit Statistic	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N= N_{EVAL}
Brain Natriuretic Peptide (pg/mL)			
Week 6 Change from baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 12 Change from baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 18 Change from baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 24 Change from baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
NYHA Heart Failure Classification			
Week 6 Change from baseline			
2 class improvement	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
1 class improvement	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
None	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
1 class decline	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
2 class decline	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Week 12 Change from baseline			
2 class improvement	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)

Secondary Endpoints
Cardiac Function
Change from Baseline Summary

Parameter Visit Statistic	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N= N_{EVAL}
1 class improvement	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
None	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
1 class decline	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
2 class decline	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Week 18 Change from baseline			
2 class improvement	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
1 class improvement	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
None	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
1 class decline	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
2 class decline	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Week 24 Change from baseline			
2 class improvement	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
1 class improvement	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
None	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
1 class decline	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
2 class decline	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)

Secondary Endpoints
Cardiac Function
Longitudinal Model Results

Parameter	Slope Estimate with 95% CI		Difference of A vs. B		
Time Interval	Treatment A	Treatment B	Estimate with 95% CI	z Value	P-Value
Brain Natriuretic Peptide (pg/mL)					
Week 0-6	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 0-12	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 12-24	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 0-24	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
NYHA Heart Failure Classification					
Week 6 CFB	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 12 CFB	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 18 CFB	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 24 CFB	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx

Secondary Endpoints
Quality of Life
Descriptive Summary

Parameter Visit Statistic	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N= N_{EVAL}
UCSD Shortness of Breath Questionnarie Total Score			
Baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 6			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 12			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 18			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 24			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)

Secondary Endpoints
Quality of Life
Change from Baseline Summary

Parameter Visit Statistic	Treatment A N= N_{EVAL}	Treatment B N= N_{EVAL}	All Patients N= N_{EVAL}
UCSD Shortness of Breath Questionnarie Total Score			
Week 6 Change from baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 12 Change from baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 18 Change from baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Week 24 Change from baseline			
N (Missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)

Secondary Endpoints
Quality of Life
Longitudinal Model Results

Parameter	Slope Estimate with 95% CI		Difference of A vs. B		
Time Interval	Treatment A	Treatment B	Estimate with 95% CI	z Value	P-Value
UCSD Shortness of Breath Questionnarie Total Score					
Week 0-6	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 0-12	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 12-24	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Week 0-24	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx

Serious Adverse Events
Treatment A

Patient ID	Start Date	Study Period	Lower Level Term	Action Taken with Study Drug	Causal Relationship	Outcome	Unexpected
XXXXXX	DDMMMYYYY	Double Blind	<<Lower Level Term Text>>	None	Not a reasonable possibility	Resolved no squelae	Yes
	DDMMMYYYY	Double Blind	<<Lower Level Term Text>>	Discontinued	Reasonable possibility	Resolved with squelae	
	DDMMMYYYY	Open Label	<<Lower Level Term Text>>	Dose altered	Not a reasonable possibility	Unresolved	
XXXXXX	DDMMMYYYY	Double Blind	<<Lower Level Term Text>>	None	Not a reasonable possibility	Unresolved	Yes
XXXXXX	DDMMMYYYY	Open Label	<<Lower Level Term Text>>	Interrupted	Not a reasonable possibility	Patient died	Yes

Serious Adverse Events
Treatment B

Patient ID	Start Date	Study Period	Lower Level Term	Action Taken with Study Drug	Causal Relationship	Outcome	Unexpected
XXXXXX	DDMMMYYYY	Double Blind	<<Lower Level Term Text>>	None	Not a reasonable possibility	Resolved no squelae	Yes
	DDMMMYYYY	Double Blind	<<Lower Level Term Text>>	Discontinued	Reasonable possibility	Resolved with squelae	
	DDMMMYYYY	Open Label	<<Lower Level Term Text>>	Dose altered	Not a reasonable possibility	Unresolved	
XXXXXX	DDMMMYYYY	Double Blind	<<Lower Level Term Text>>	None	Not a reasonable possibility	Unresolved	Yes
XXXXXX	DDMMMYYYY	Open Label	<<Lower Level Term Text>>	Interrupted	Not a reasonable possibility	Patient died	Yes

Non Serious Adverse Events
Treatment A

Patient ID	Start Date	Duration (Weeks)	Study Period	Lower Level Term	Maximum Intensity	Relationship to Study Drug	Action Taken with Study Drug	Final Outcome
XXXXXX	DDMMMYYYY	xx.x	Double Blind	<<Preferred Term Text>>	Mild	Not a reasonable possibility	None	Resolved no squelae
	DDMMMYYYY	xx.x	Double Blind	<<Preferred Term Text>>	Moderate	Reasonable possibility	Discontinued	Resolved with squelae
	DDMMMYYYY	xx.x	Open Label	<<Preferred Term Text>>	Severe	Not a reasonable possibility	Dose changed	Unresolved
XXXXXX	DDMMMYYYY	xx.x	Double Blind	<<Preferred Term Text>>	Severe	Not a reasonable possibility	None	Unresolved
XXXXXX	DDMMMYYYY	xx.x	Open Label	<<Preferred Term Text>>	Severe	Not a reasonable possibility	Interrupted	Patient died

Non Serious Adverse Events
Treatment B

Patient ID	Start Date	Duration (Weeks)	Study Period	Lower Level Term	Maximum Intensity	Relationship to Study Drug	Action Taken with Study Drug	Final Outcome
XXXXXX	DDMMMYYYY	xx.x	Double Blind	<<Preferred Term Text>>	Mild	Not a reasonable possibility	None	Resolved no squelae
	DDMMMYYYY	xx.x	Double Blind	<<Preferred Term Text>>	Moderate	Reasonable possibility	Discontinued	Resolved with squelae
	DDMMMYYYY	xx.x	Open Label	<<Preferred Term Text>>	Severe	Not a reasonable possibility	Dose changed	Unresolved
XXXXXX	DDMMMYYYY	xx.x	Double Blind	<<Preferred Term Text>>	Severe	Not a reasonable possibility	None	Unresolved
XXXXXX	DDMMMYYYY	xx.x	Open Label	<<Preferred Term Text>>	Severe	Not a reasonable possibility	Interrupted	Patient died